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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <b>(54) Title:</b> CYTOKINE COMBINATION THERAPY<br><br><b>(57) Abstract</b><br><br>This invention relates to methods of treatment of persons and animals with indications of immuno-deficiency, wherein the said indication is resultant from viral and/or retroviral, bacterial, fungal or parasitic infection and/or plus infectious protein units. Herein is described the method of administration of an agonist or antagonist to Th <sub>2</sub> cytokines in combination with anti-viral agents or immune enhancing agents. In one aspect of the invention, the agonist or antagonist is a receptor to Interleukin-4 (or mutein receptor) which is administered in combination with an anti-viral agent. Preferred anti-viral/immune-enhancing agents include (a) "compounds of Formula I" (defined herein), and metabolites, analogs and precursors thereof, and pharmaceutically acceptable salts of any such compounds, metabolites, analogs and precursors, (b) protease inhibitors, and (c) reverse transcriptase inhibitors. Additionally herein is described a method of enhancing viral replication as a means of exposing latent infection by the administration of an agonist or antagonist to a Th <sub>2</sub> cytokine. There are also provided such methods comprising administering to a patient at least one Th <sub>2</sub> cytokine and at least one agonist and/or at least one antagonist to said Th <sub>2</sub> cytokine. There are also provided compositions and kits for use in such methods, as well as the use of such compounds in the manufacture of medicaments for treatment for various conditions. |           |   |

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## CYTOKINE COMBINATION THERAPY

### Field of the Invention

This invention relates to methods of treatment of patients for enhancing immune response, treating viral infection (including retroviral infection), bacterial infection, fungal infection, parasitic infection and/or infectious protein units in a patient in need of such treatment, or minimizing the likelihood of such infection and/or reducing the potential future adversity of such infection in a patient. The invention further relates to methods of providing immunosuppressive or immunoregulatory effects in a patient. The invention further relates to the use of compounds in the manufacture of medicaments for use in treating a variety conditions, as well as compositions and kits containing the active materials according to the present invention.

### Background of the Invention

The Human Immunodeficiency Virus Type I (HIV- I) is the etiological agent of Acquired Immune Deficiency Syndrome (AIDS). AIDS is characterized as a profound breakdown in host's cellular and humoral immunity and increased susceptibility to a wide range of opportunistic infections. One of the consequences of this immune dysfunction is a marked depletion in absolute CD4+ cells in HIV-infected individuals.

The HIV protease enzyme is responsible for post translational processing of *gag* and *gag-pol* polyprotein precursors into their functional products. This aspartyl type protease has been identified as a potential target for antiretroviral therapy, as inhibition of the enzyme results in the production of immature non-infectious virions and subsequent interruption of viral spread.

### Summary of the Invention

In accordance with one aspect of the present invention, there are provided methods of treatment of a patient for enhancing immune response, comprising administering to the patient (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine.

In accordance with another aspect of the present invention, there are provided methods of treating viral infection (including retroviral infection), bacterial infection, fungal infection, parasitic infection and/or infectious protein units in a patient, or minimizing the likelihood of such infection and/or reducing the potential future adversity of such infection in a patient, comprising administering to the patient (1) at least one

anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine..

Another aspect of the present invention relates to methods of providing immunosuppression or immunoregulatory effect a in patient, comprising administering to the patient (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine.

The present invention provides methods of treatment of persons and animals with indications of immuno-deficiency, wherein the said indication is resultant from viral and/or retroviral, bacterial, fungal or parasitic infection and/or plus infectious protein units. Herein is described the method of administration of an agonist or antagonist to Th<sub>2</sub> cytokines in combination with anti-viral agents or immune enhancing agents. In one aspect of the invention, the agonist or antagonist is a receptor to Interleukin-4 (or mutein receptor) which is administered in combination with an anti-viral agent. Preferred anti-viral/immune-enhancing agents include (a) "compounds of Formula I" (defined below), and metabolites, analogs and precursors thereof, and pharmaceutically acceptable salts of any such compounds, metabolites, analogs and precursors, (b) protease inhibitors, and (c) reverse transcriptase inhibitors. Additionally herein is described a method of enhancing viral replication as a means of exposing latent infection by the administration of an agonist or antagonist to a Th<sub>2</sub> cytokine.

Also described herein is a method of administration of an agonist or antagonist to Interleukin-4, e.g., preferably a receptor to IL-4 (Interleukin-4), is administered in combination with one or more anti-viral agents for viral treatment. Additionally herein is described a novel treatment regimen which enhances viral replication, thus allowing more effective protease enzyme inhibition wherein the viral enhancing pharmaceutical agent is part of a combination therapy with protease inhibitors and/or reverse transcriptase inhibitors.

The present invention further relates to methods of reducing proviral DHA in patients, and/or facilitating transport into immune cells.

The present invention stems from the novel discovery that peptide/glycopeptide sequences exhibited as components of immature non-infectious virions coat proteins or glycoproteins act in a deleterious manner to human and animal biological functions by binding specifically to the receptor molecules of certain Th<sub>2</sub> cytokines. The presence

of these peptides, polypeptides/glycopeptide sequences which facilitate binding to receptor molecules to Th<sub>2</sub> cytokines is the essential factor, which allows these classes of virions both infectious and non-infectious to inhibit improved immune response. This discovery opens new avenues to treatment and/or prevention by inoculation or therapy of immunosuppressive disorders and/or viral, certain bacterial and/or mycoplasma infections.

Another aspect of this invention relates to combination therapies, one component of which is an agonist or an antagonist to a Th<sub>2</sub>, e.g., agonist or antagonist to IL-4, for therapy against indications/disease caused by viral agents. hIL-4 is produced by T-cells and acts as a growth factor for pre-activated B-cells and T-cells. It acts on enriched B-cell populations to produce IgE and on purified B-cells to secrete IgG and IgM. It enhances the generation of cytotoxic T-cells but inhibits the IL-2 (Interleukin-2) dependent generation of lymphocyte-activated killer cells. hIL-4 shows numerous growth and differentiation promoting effects on other hemopoietic lineages. IL-4 elicits its biological activities by binding to specific receptors on the cell surface of IL-4 responsive cells. Binding of IL-4 to its receptor causes rapid receptor internalisation followed by up-regulation of IL-4 receptor expression in the case of a human B lymphoma, human tonsillar B-cells, and mouse T- and B-cells.

This invention further relates to methods of treatment of persons and animals with indications of immuno-deficiency, wherein the said indication is resultant from viral and/or retroviral infection and/or infectious protein units originating from bacterial, fungal or parasitic sources.

In accordance with one aspect of the present invention, there is provided a combination therapy in which (1) one or more anti-viral agent, and (2) recombinant receptor to IL-4, are administered (individually or in any combinations) to a patient to bring about a reduction in the level of proviral DNA (i.e., latent viral cells in the patient's circulation). In a further preferred aspect of the present invention, there is provided a combination therapy in which (1) one or more anti-viral agent, (2) recombinant receptor to IL-4, and (3) IL-4 are administered (individually or in any combinations) to a patient to bring about a reduction in the level of proviral DNA. Where IL-4 is administered in addition to recombinant receptor to IL-4, there is often obtained a further sustainment of reduction in proviral DNA, because this treatment avoids depletion of the patient's

IL-4 resulting from the administration of recombinant receptor to IL-4. Furthermore, binding of recombinant receptor to IL-4 with IL-4 makes it acceptable into immune cells by facilitating transport into the immune cells.

Our studies have established the functional binding and immunosuppressive similarities between certain HIV envelope glycoproteins and specific human Th<sub>2</sub> cytokines.

The acquired immunodeficiency syndrome (AIDS) is characterised by a profound immune dysfunction and opportunistic infections. The immunologic abnormalities include not only the T-helper/inducer lymphocyte subset but also most if not all the major cellular components of the immune system including B lymphocytes, monocytes/macrophages, natural killer cells (NK), and others. Therefore, it is reasonable to expect that in addition to a selective depression of CD4 helper lymphocytes, there exists additional immunoregulatory mechanisms involved in the observed immunodepression of HIV.

Abnormalities in NK (Natural Killer) cell activity have been reported in AIDS patients in spite of an apparently normal number of circulating NK cells. The activity of cell-mediated defence systems is stimulated by consecutive formulation of Interleukin 1 $\beta$  (IL-1 $\beta$ ), Interleukin-2 (IL-2) and Interferon  $\gamma$  (IFN  $\gamma$ ). The system is inhibited by Interleukin-4 (IL-4) and also by prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and histamine, which are released when the immune system is activated.

Interleukin-4 also presents in the transmembrane amino acid sequences of certain viruses including HIV which allow the full vigilance of the immune system to be deflected to a Th<sub>2</sub> system allowing infection to gain a hold and avoid complete viral clearance.

HIV envelope glycoprotein is synthesised as a polyprotein precursor of 160 kDa (gp 160) and is subsequently cleaved into an amino terminus subunit, gp 120, and a carboxy terminus transmembrane subunit, gp41. Lymphocytes from AIDS patients have been reported to secrete a protein with immunosuppressive properties. Mitogen- and antigen-driven blastogenic responses have been shown to be inhibited by purified HIV preparations.

The immunosuppressive properties, including the inhibition of normal human NK cell activity, of the FeL V transmembrane glycoprotein P15E and the suppression of

mitogen- and alloantigen-induced lymphocyte blastogenesis by HIV synthetic peptides 735-752 and 846-860 corresponding to sequences within the HIV transmembrane gp41. Both these transmembrane HIV peptides were found to have a significant inhibitory effect on NK cell activity, even at doses as low as 0.1 µg/ml.

5 One of the mechanisms by which the immune system normally regulates itself includes the production of proteins called cytokines. For example, lymphokines are cytokines produced by T-cells and some B-cells, and monokines are cytokines produced by monocytes. Cytokines, which may be glycosylated, mediate numerous immune responses.

10 IL-4 is a cytokine capable of stimulating production of antibody producing B-cells and which also promotes growth of killer T-cells or cytotoxic T-cells. Additionally, it can inhibit the activity of T-helper cells type 1 (Th1). This in turn may inhibit production of more B-cells or antibody production by more B-cells. Thus, IL-4 is part of an internal regulatory mechanism. A selection of amino acid sequences prepared according to our  
15 sequences have demonstrated in a dose dependent manner the ability to down-regulate the expression of Ia molecules on human macrophages similar to Interleukin-4. Some in-vitro experiments suggest that direct T-cell antigen interactions without the mediation of Ia bearing macrophages may result in the generation of antigen specific suppressor T-cells. All experimental evidence indicates that the development of  
20 antigen-reactive clones of helper T-cells requires the presence of Ia bearing cells in the tissue. This inhibition of expression on the membrane surface of these class II molecules (Ia) as produced with immunosuppressive cytokines signals the immune system to accept the appearance of new antigens as self to the immune system.

Incorporated herein are the following:

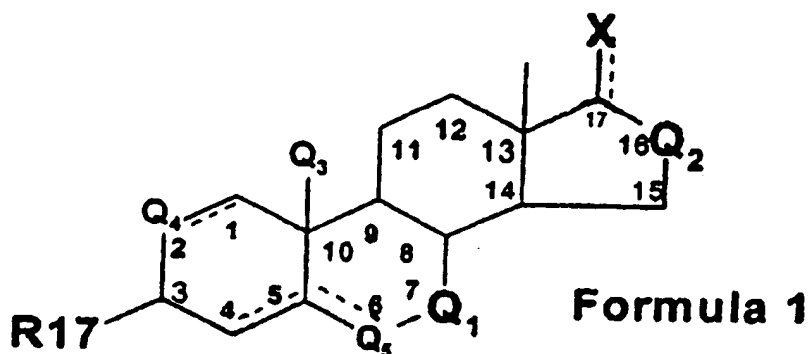
- 25 -Anti-Viral Agents as per *Rideout et al* U.S. Patent 5,086,044;  
-IL-4 Muteins as per *Lee et al* U.S. Patent 5,017,691;  
-Interleukin-4 binding protein- as per *Fanslow et al*. U.S. Patent 5,223,605;  
-Humanized Monoclonal Antibodies Against Human Interleukin-4 as per *Daliev et al* U.S. Patent 5,597,710;  
30 -Antibodies both polyclonal and monoclonal in human IL-13 [Interleukin-13] , and purified IL-13 proteins and fragments thereof as per *Culpepper et al* U.S. Patent 5,596,072;



- Anti-Viral agents as per Prendergast U.S. Patent 4,956,355;
- Compounds of the invention include muteins human and murine IL-4s, and nucleic acids which are effectively homologous to disclosed cDNAs, and/or which are capable of coding for mammalian p IL-4s muteins as per *Lee et al* U.S. Patent 5,656,266;
- Monoclonal antibodies specific to IL-4, IL-5 [Interleukin-5] , IL-6 [Interleukin-6] , and IL-10 [Interleukin-10] as per *Mosmann et al* The Journal of Immunology Vol. 145. 2036-2945. No.9 November 1, 1990;
- IL-4 Receptor Proteins as per *Mosley et al* U.S. Patent 5,599,905;
- Cytokines receptor as per *Puri et al* U.S. Patent 5,614,191; and
- Anti-Viral Agents as per *Prendergast* U.S. Patent 5,681,831.

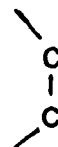
According to the present invention, there is provided agonist or antagonist to Interleukin-4, as part of a combination therapy for use in the prophylaxis and therapy of a viral infection, or a complication or consequence thereof. The viral agent may be any virus, a specific preferred example being the Human Immunodeficiency Virus.

Preferred anti-viral agents include compounds of Formula I:




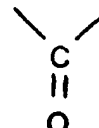
wherein  $Q_1$  is  $\begin{array}{c} \diagup \\ \text{C} \\ \diagdown \end{array}$  or  $\begin{array}{c} \diagup \\ \text{C=O} \\ \diagdown \end{array}$ ,

wherein  $Q_2$  is  $\begin{array}{c} \diagup \\ \text{C} \\ \diagdown \end{array}$ ,  $\begin{array}{c} \diagup \\ \text{C=Y} \\ \diagdown \end{array}$ , or





wherein  $Q_3$  is H or  $CH_3$

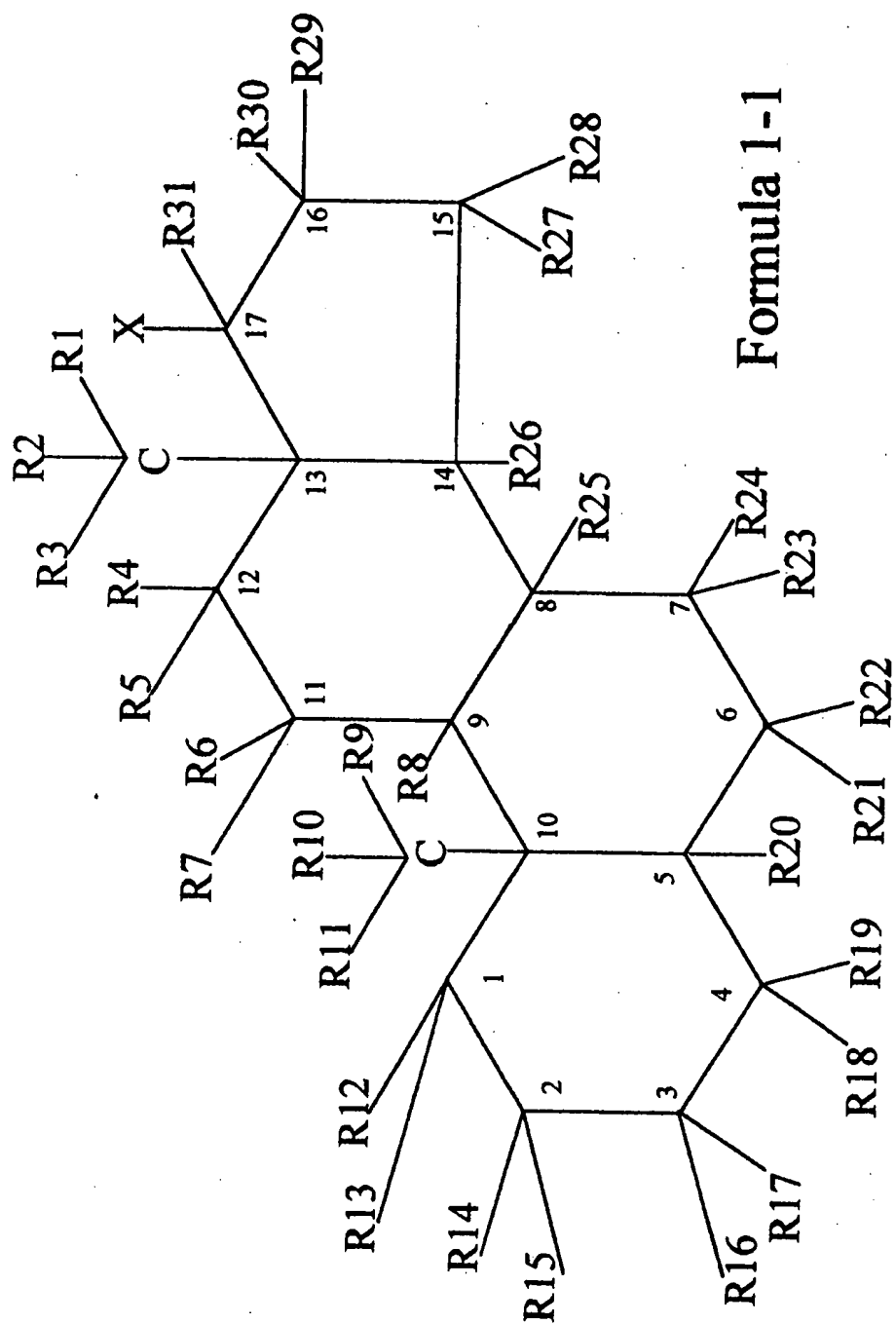
wherein  $Q_4$  is  hydroxyvinylidene, oxy or methyl methylene;

wherein  $Q_5$  is  or 

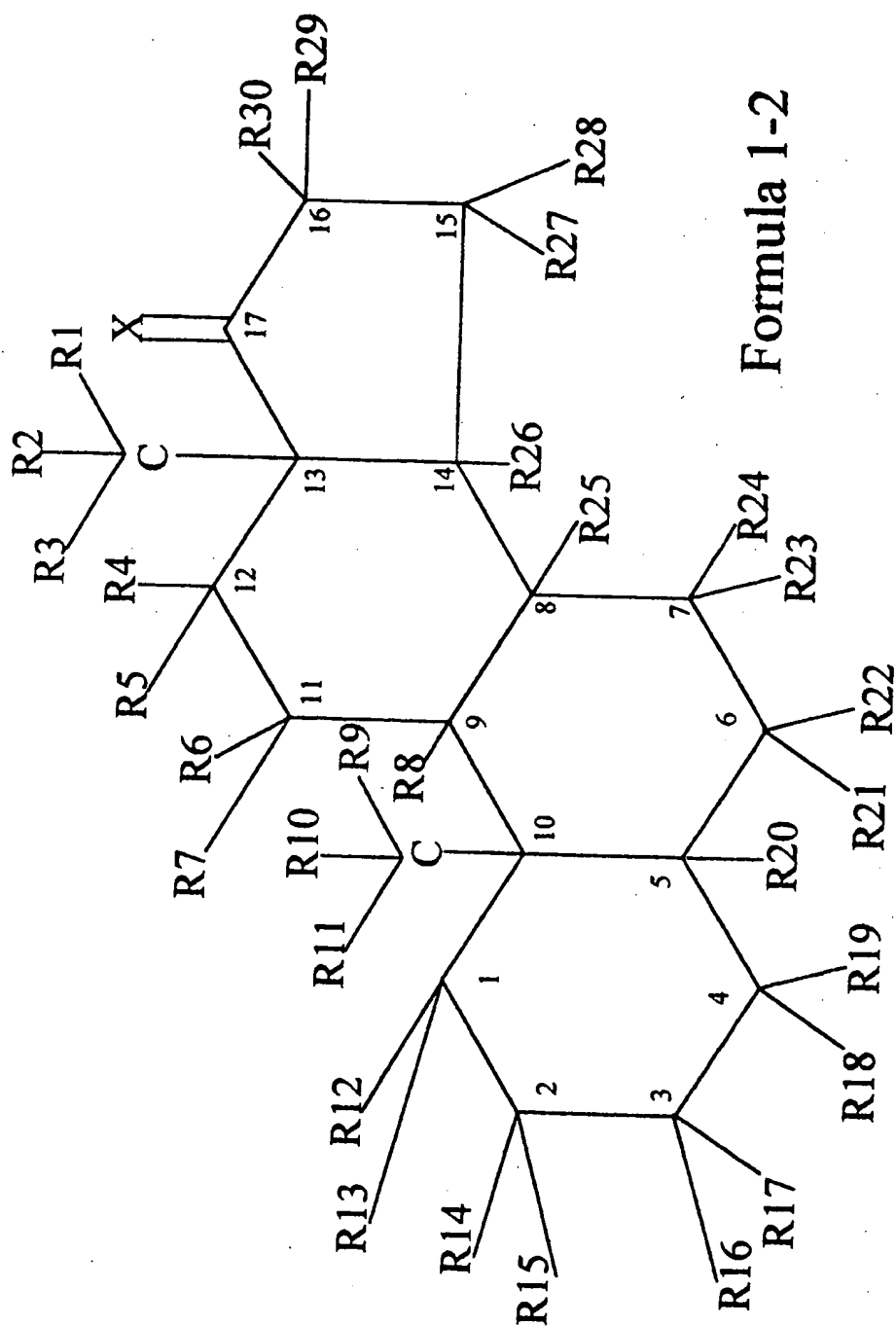
5 wherein no hydrogen atoms, some hydrogen atoms or all hydrogen atoms are independently replaced by halogen (such as Br, Cl, F or I), hydroxy,  $C_1 - C_6$  alkoxy,  $C_1 - C_6$  alkyl or  $-S-CN$ ,

10 wherein the broken lines between the 1- and 2-positions, the 4- and 5-positions and the 5- and 6- positions, as well as the broken line adjacent the 17 position (attached to X) and the broken line in the definition of  $Q_2$ , each independently (where possible, i.e., there cannot be double bonds between both the 4- and 5-position and the 5- and 6-position) represents a single bond or a double bond (where possible, where these bonds are single bonds, the alpha and/or beta configuration is present), i.e., such that in instances where: (1)  $Q_3$  is  $CH_3$ , (2) there is a double bond between the 5- and 6-positions and no double bond between the 1- and 2-positions and the 5- and 6-positions, (3)  $Q_4$  is , and (4)  $Q_5$  is , Formula 1 encompasses Formulas 1 - 1

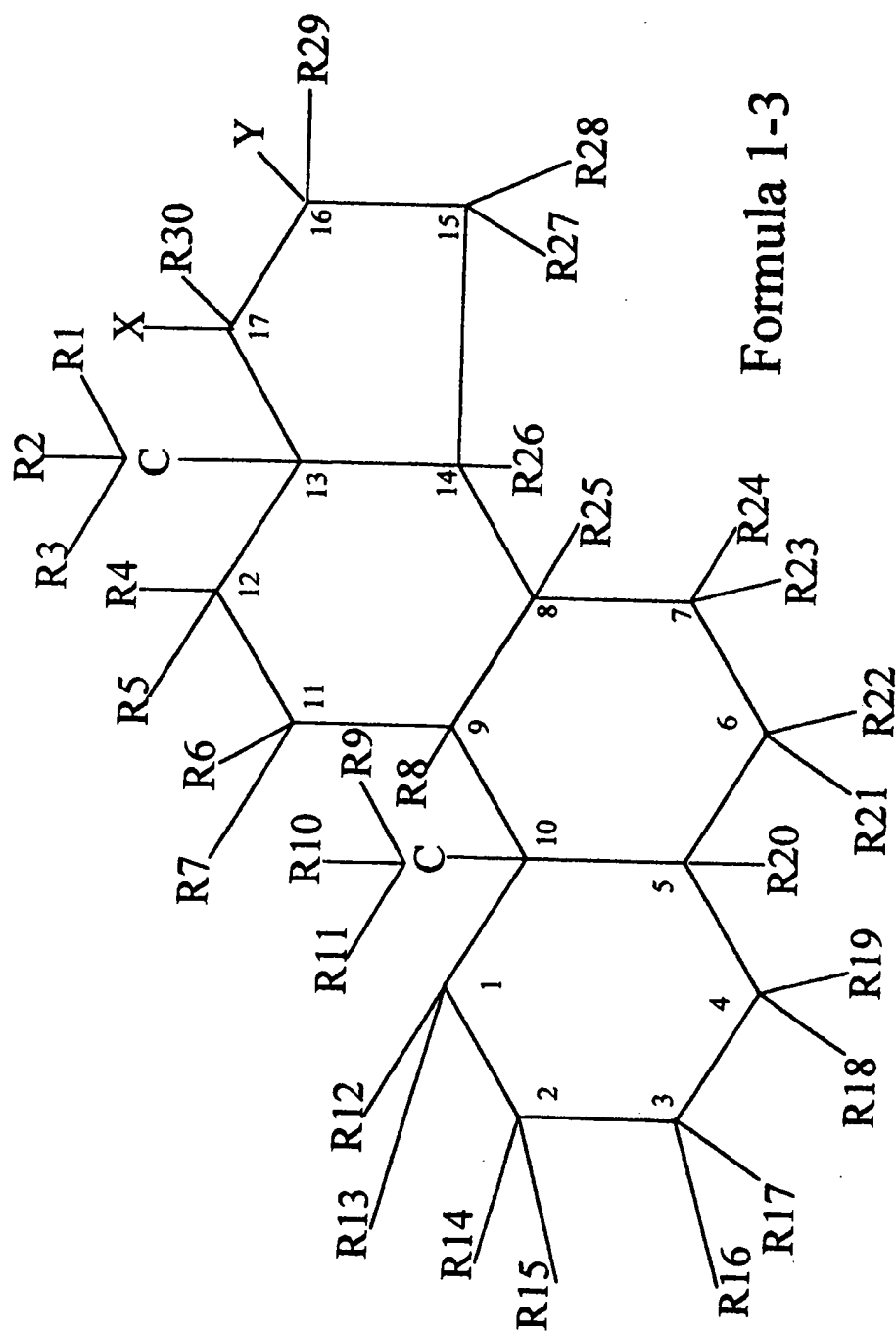
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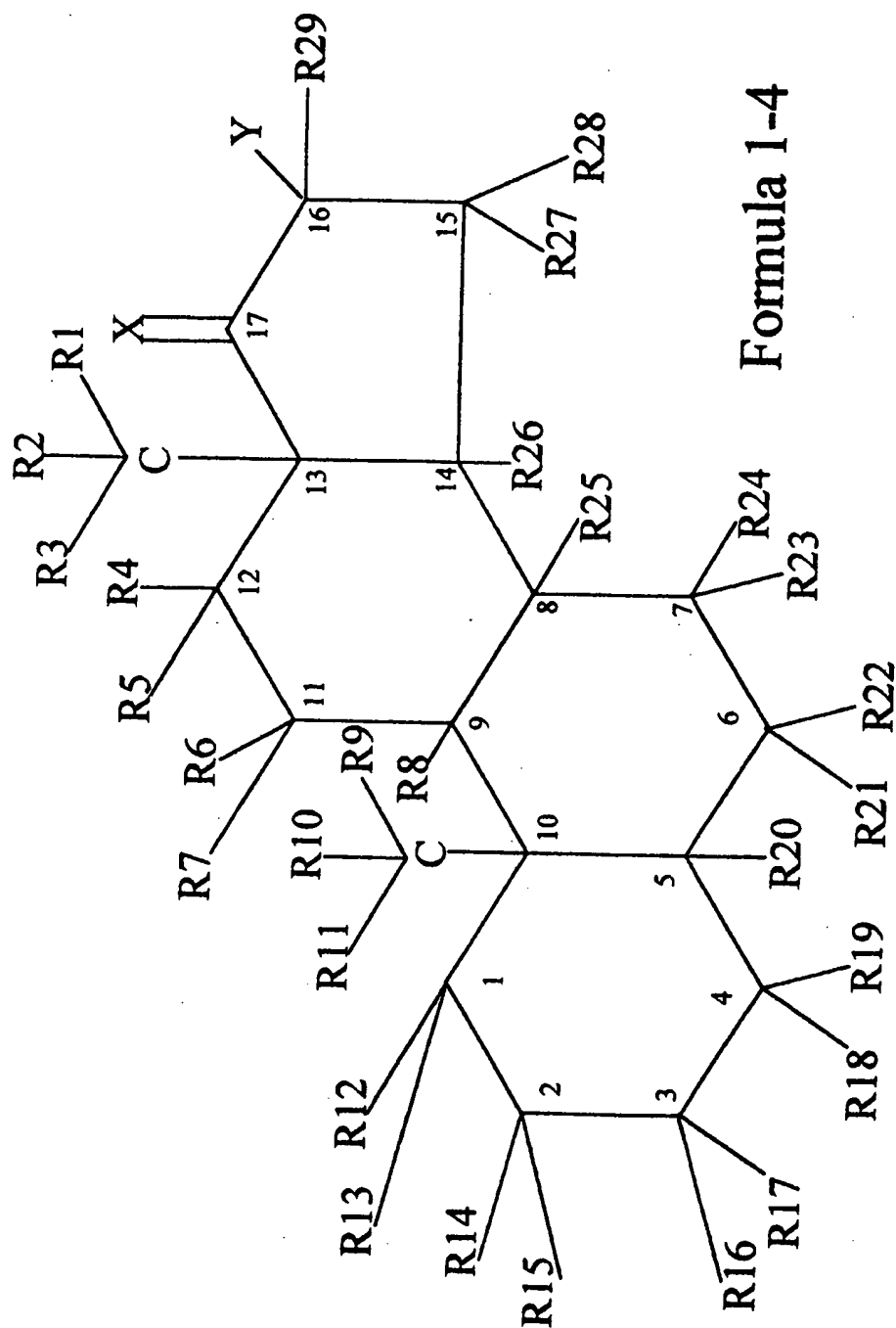
Formula 1-1



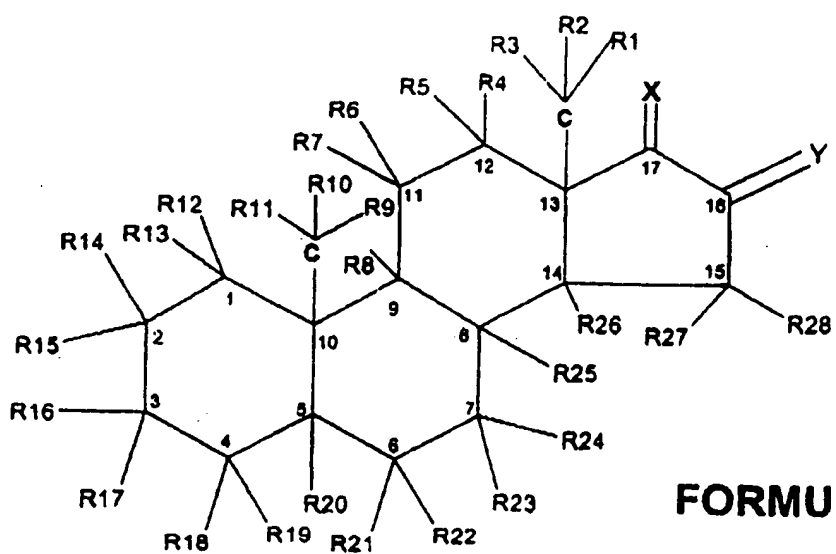
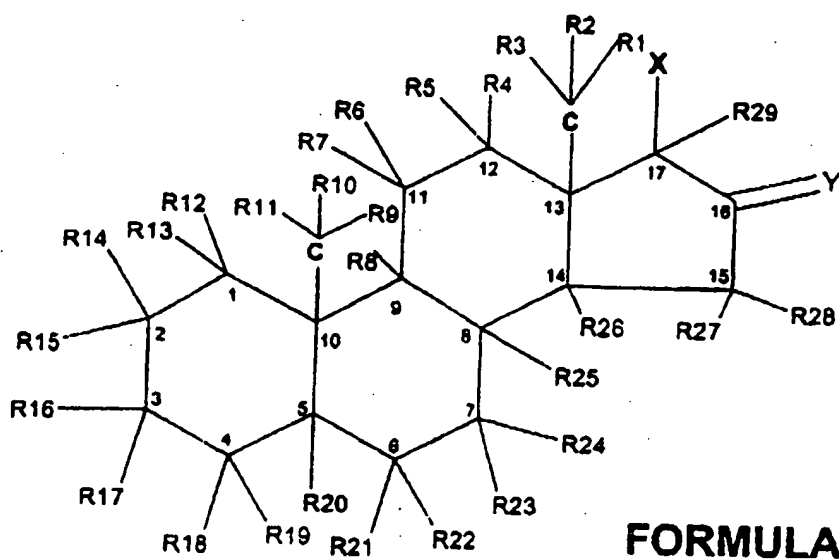
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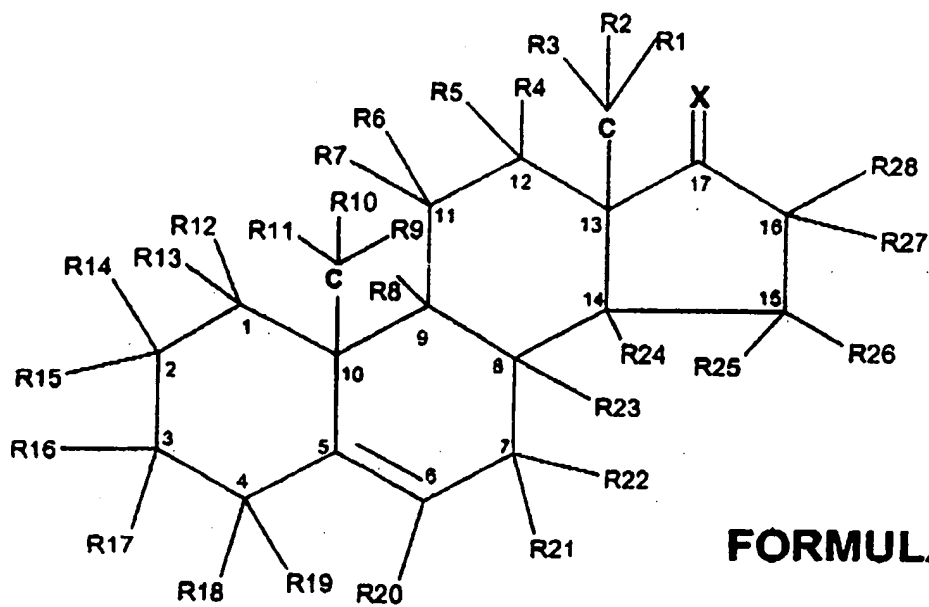
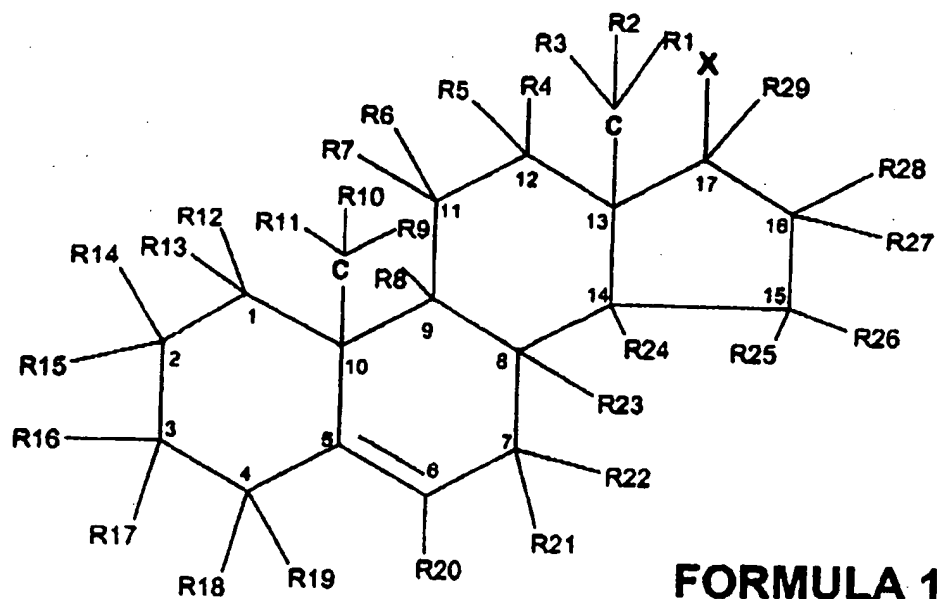


Formula 1-3

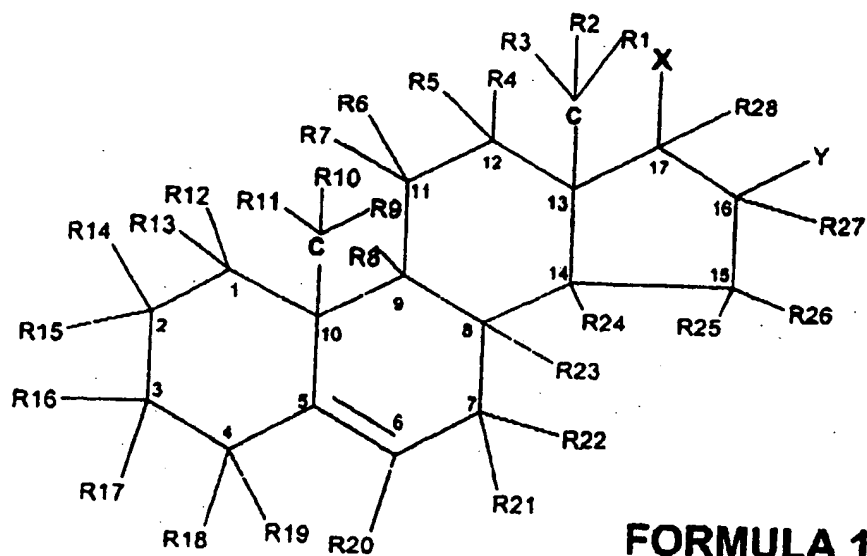
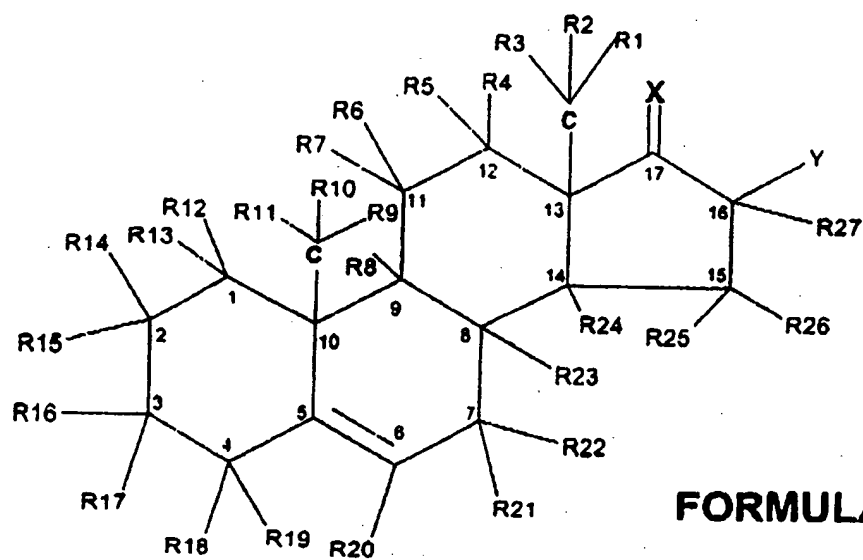


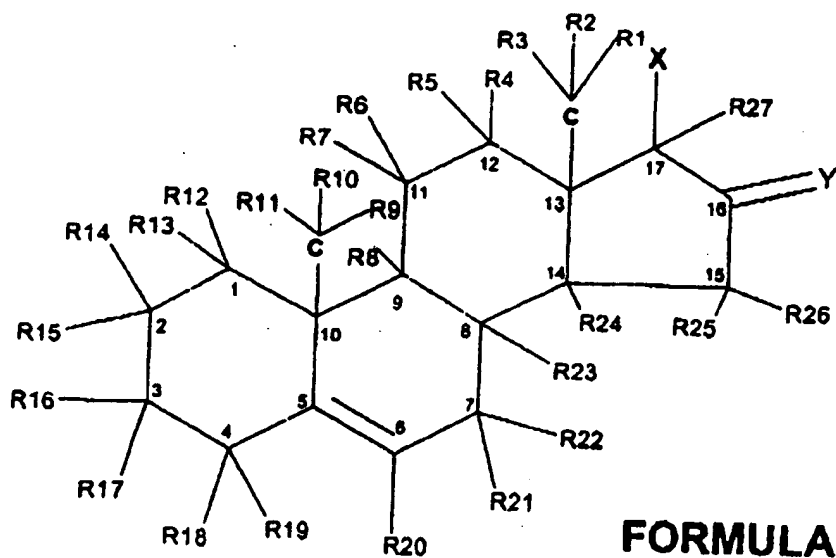
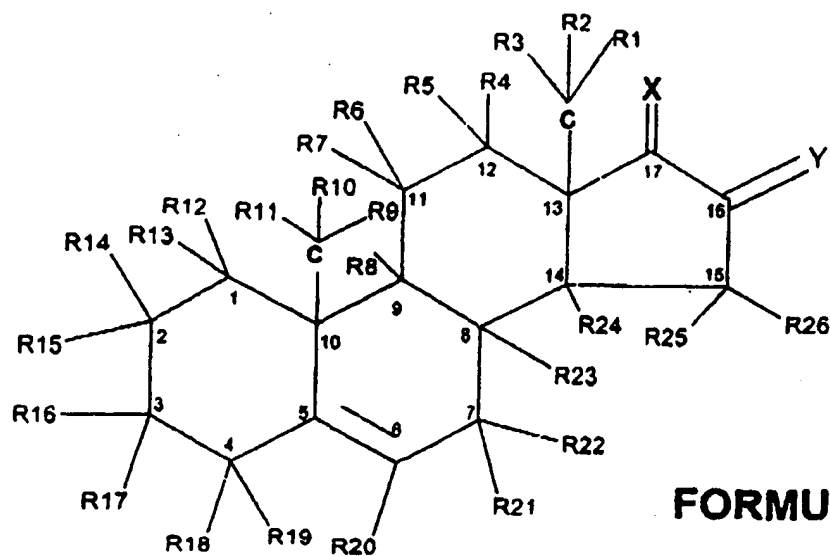
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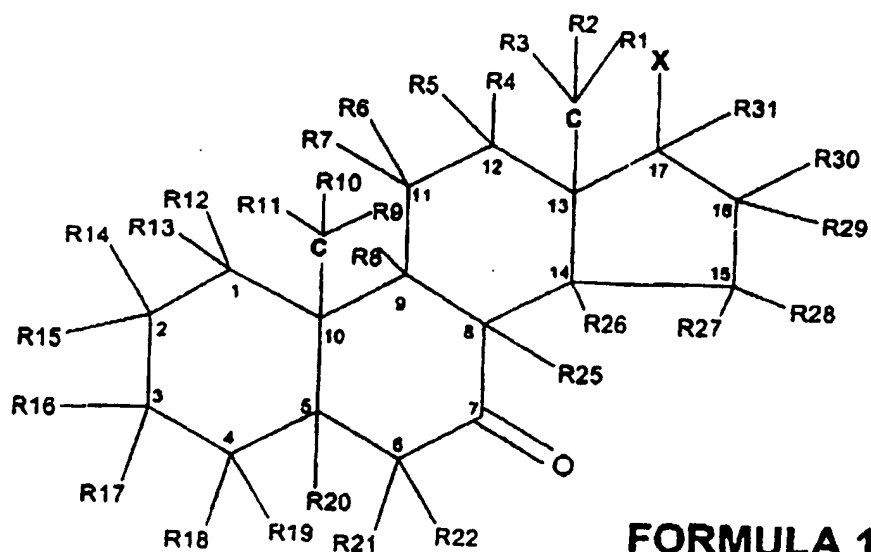
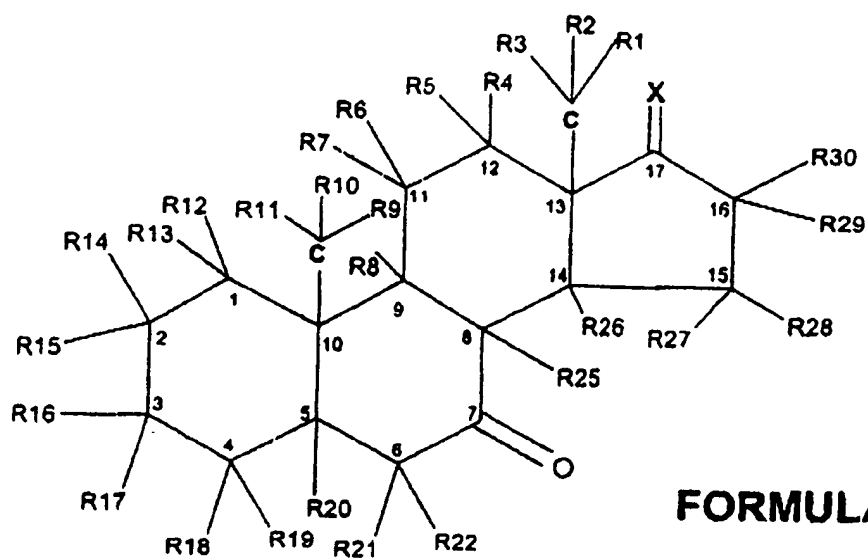


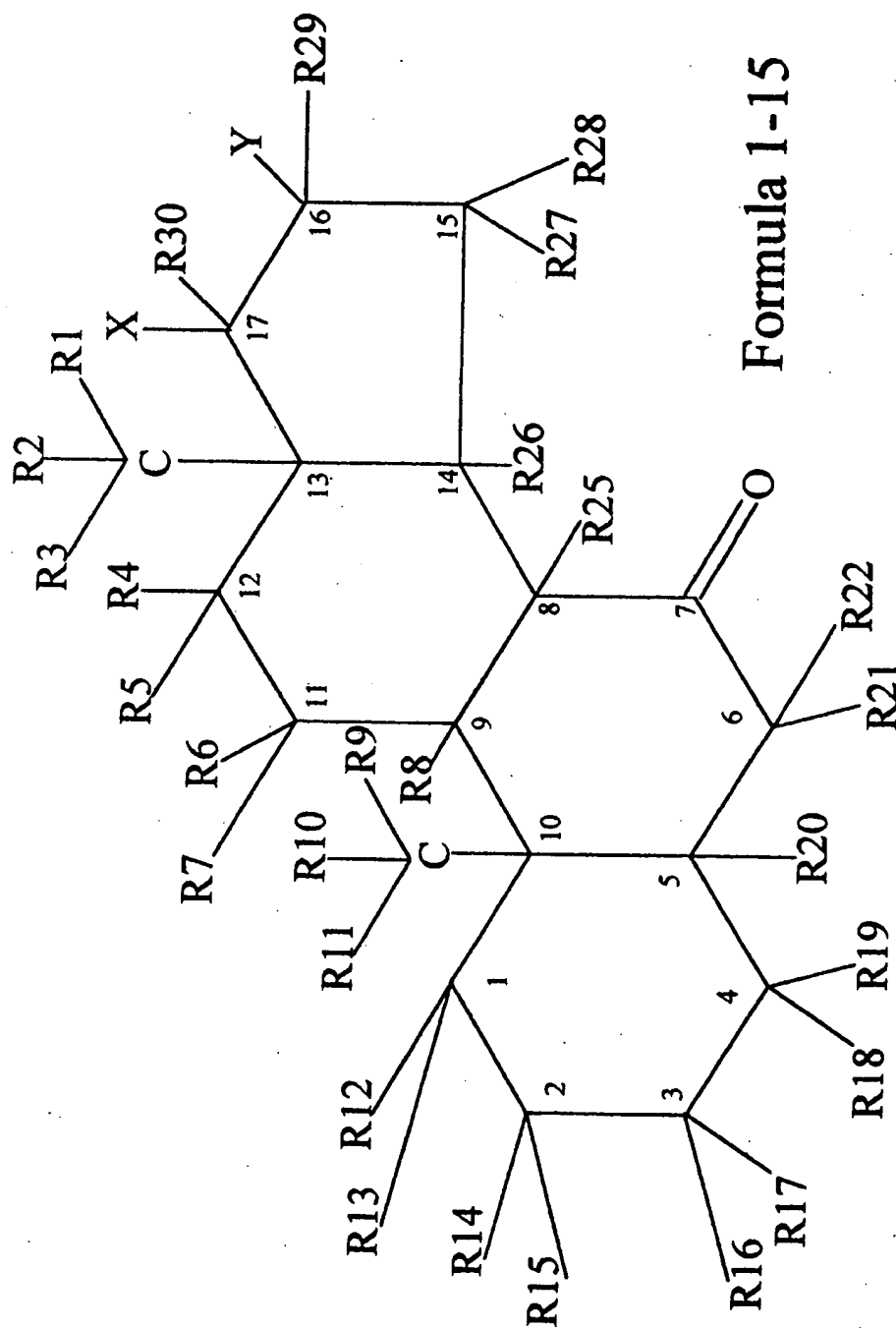




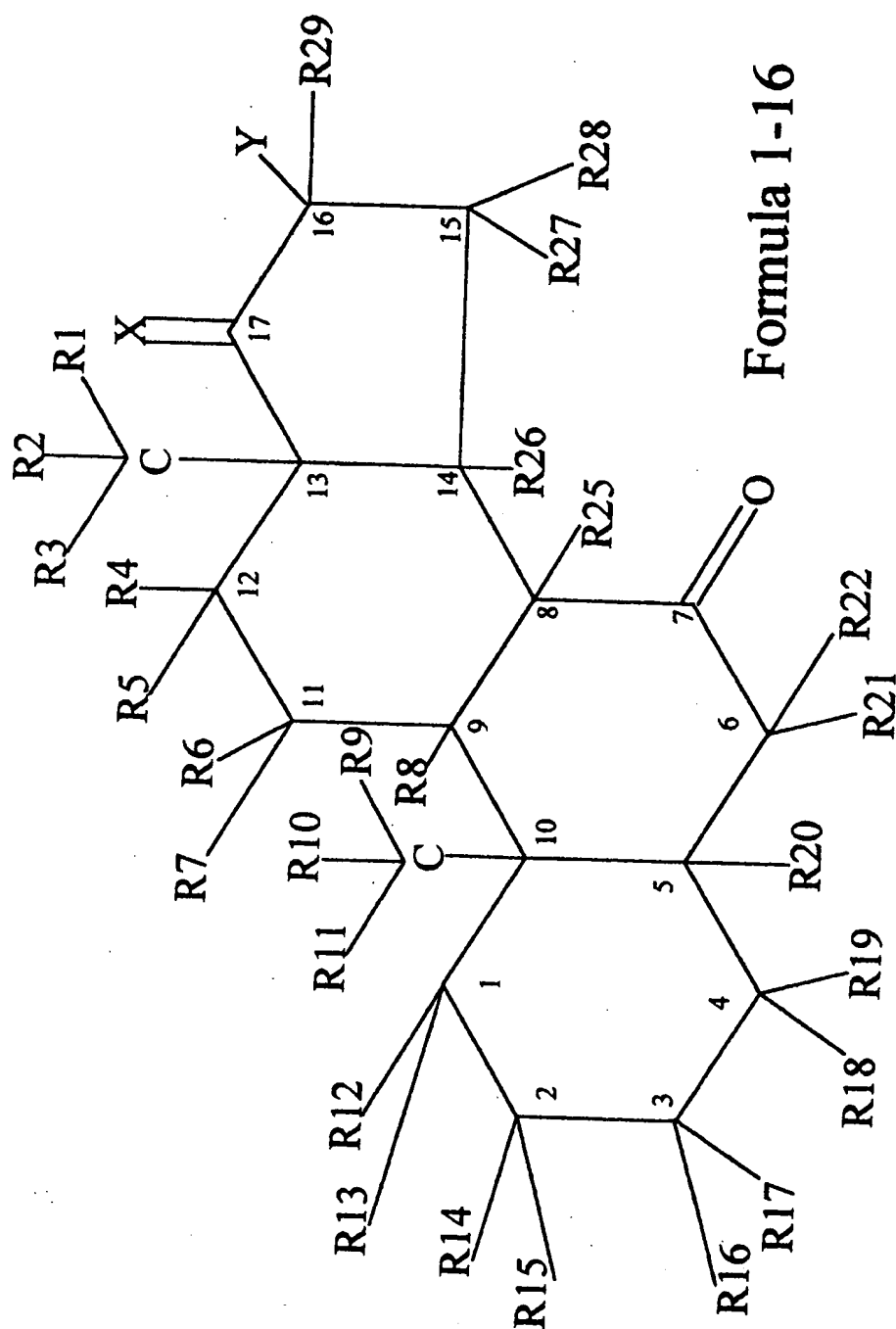
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**FORMULA 1-11****FORMULA 1-12**

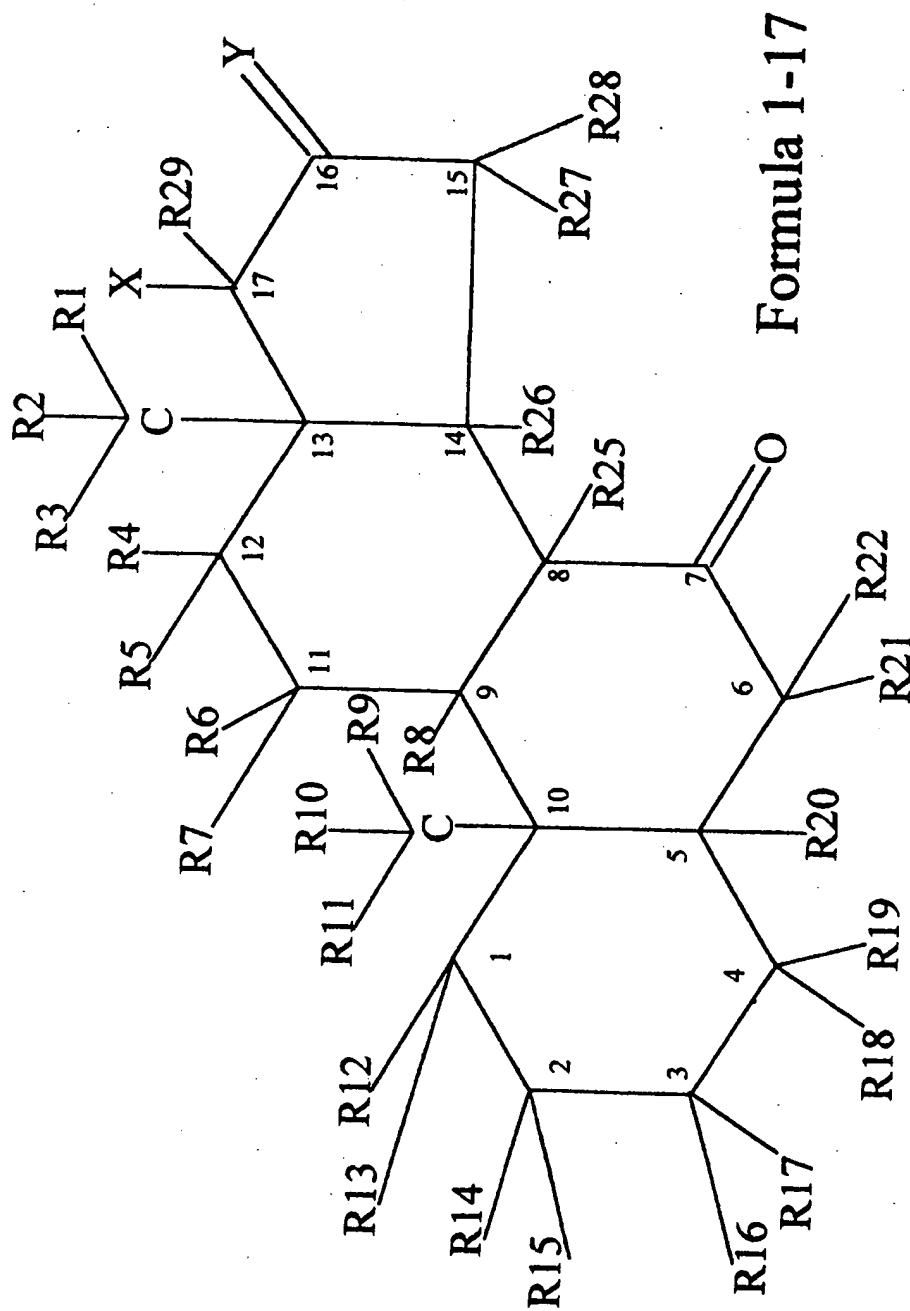
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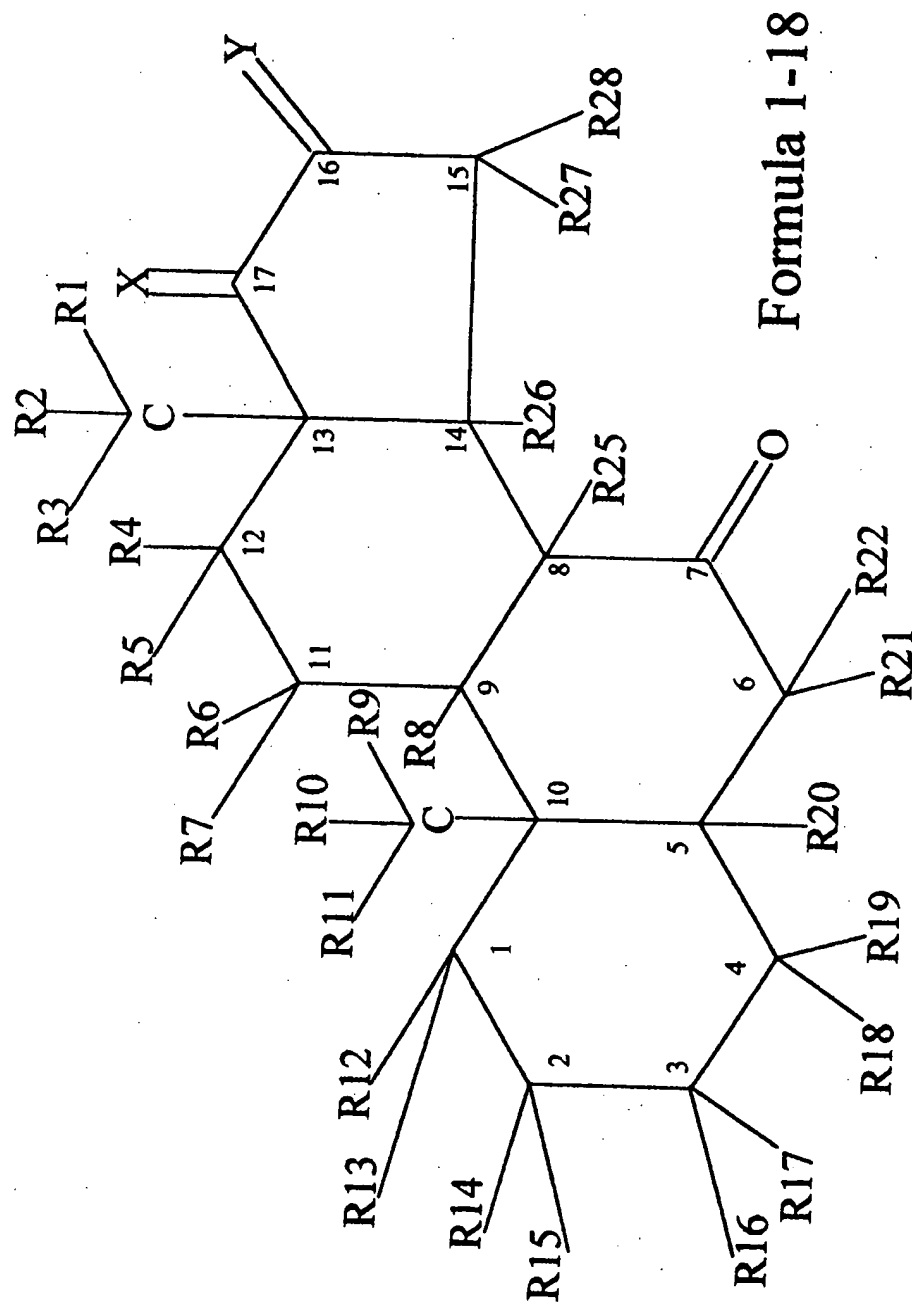
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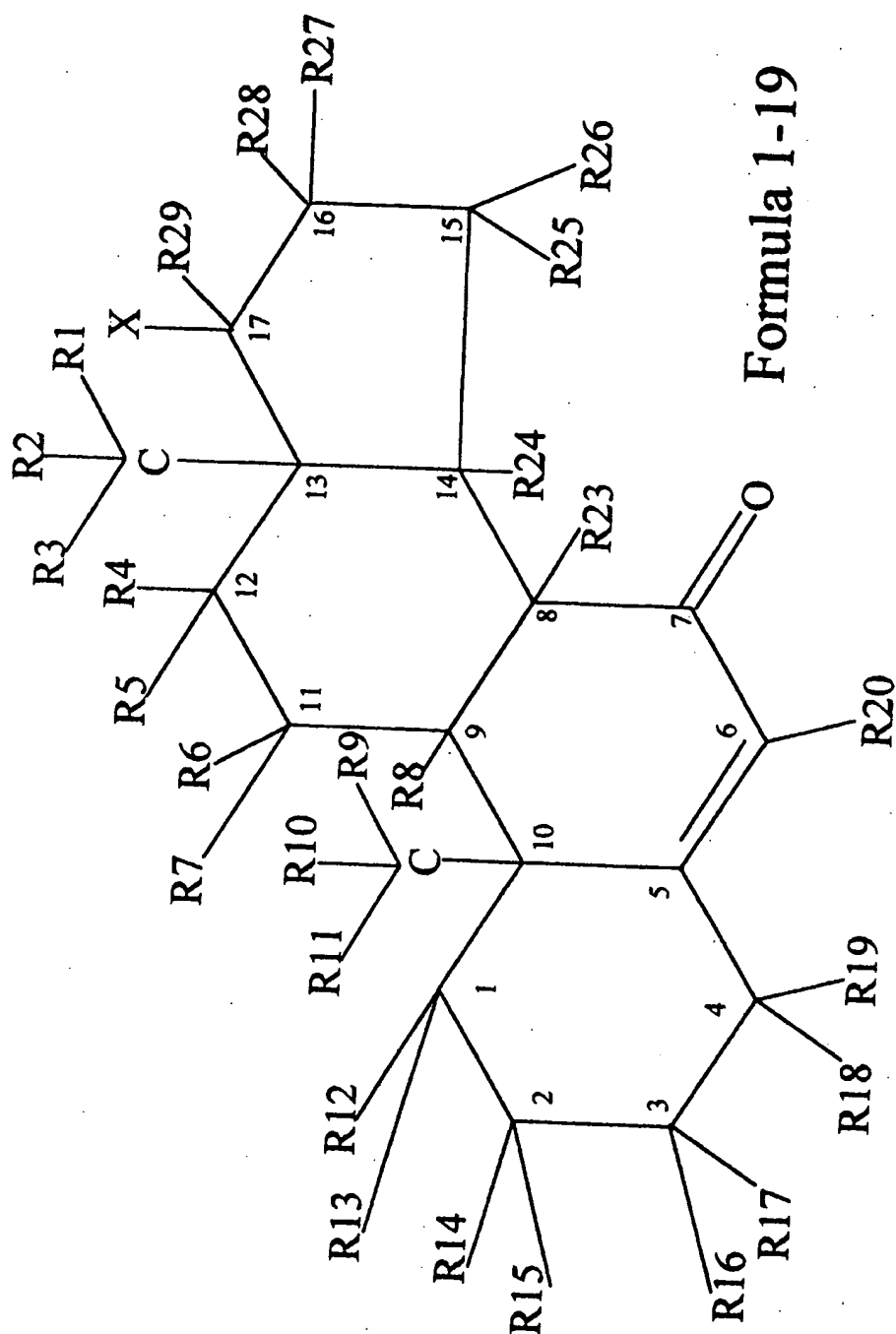
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Formula 1-17

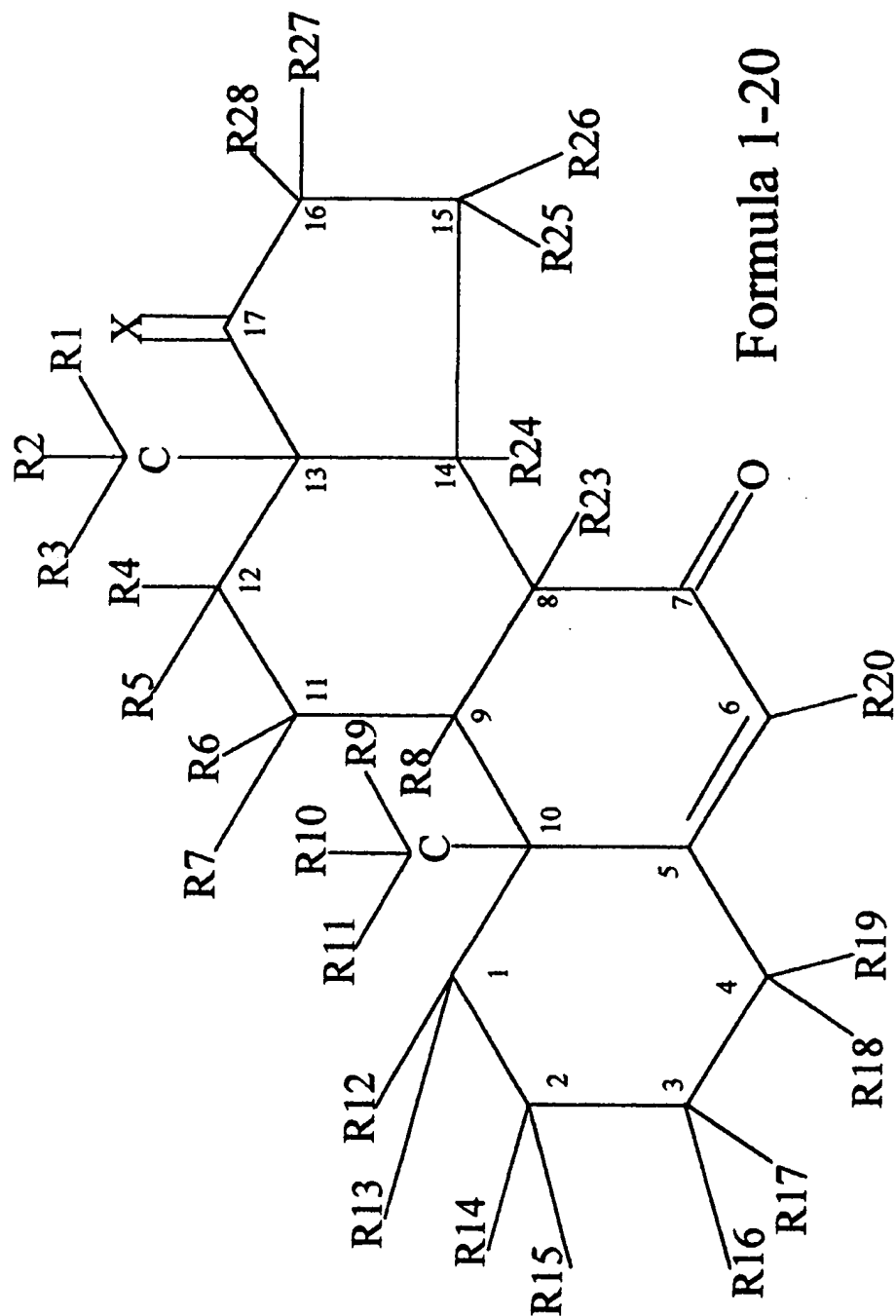


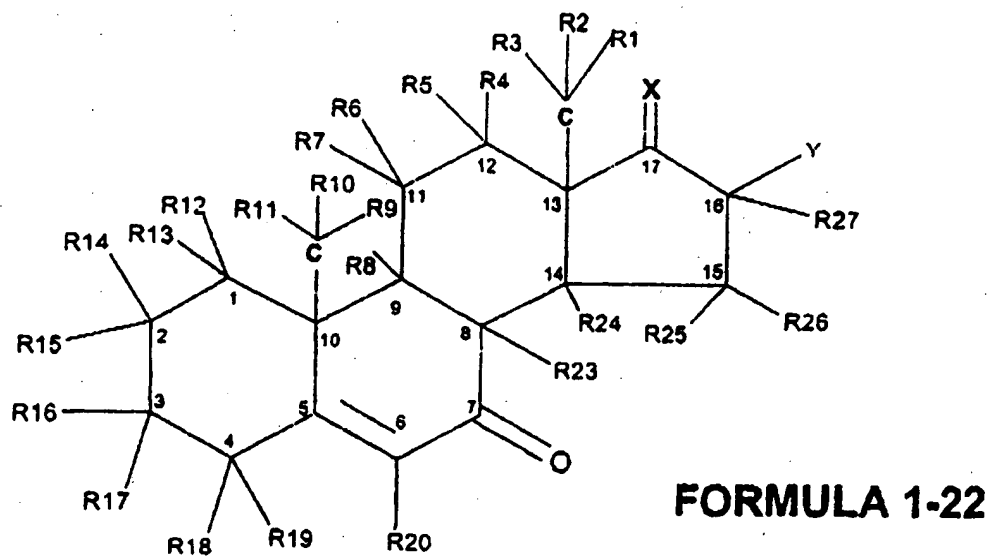
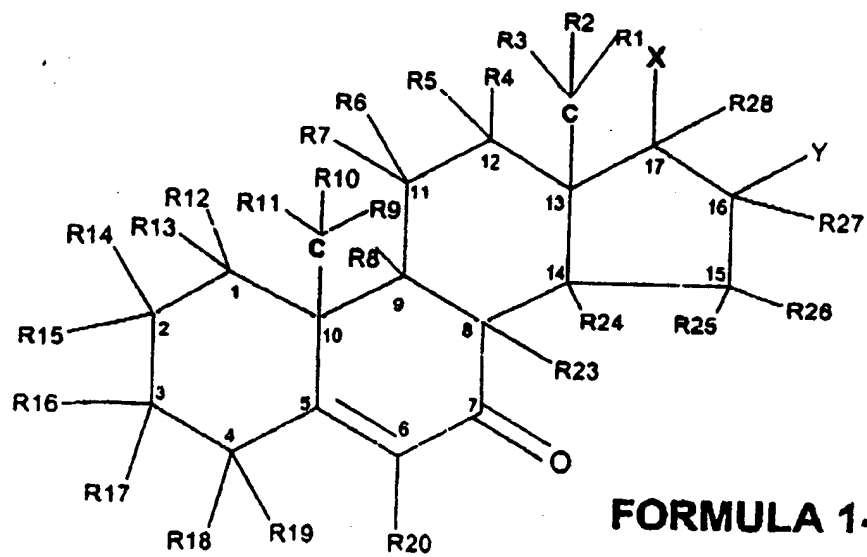
Formula 1-18

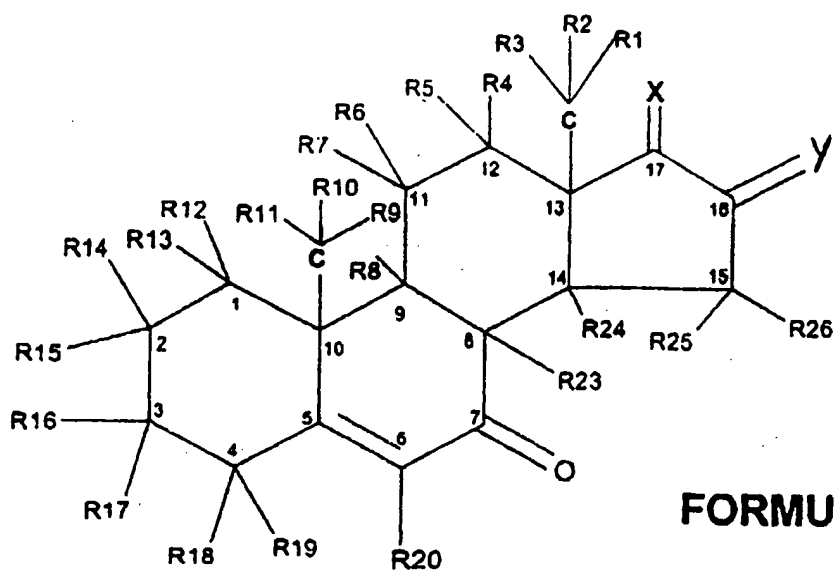
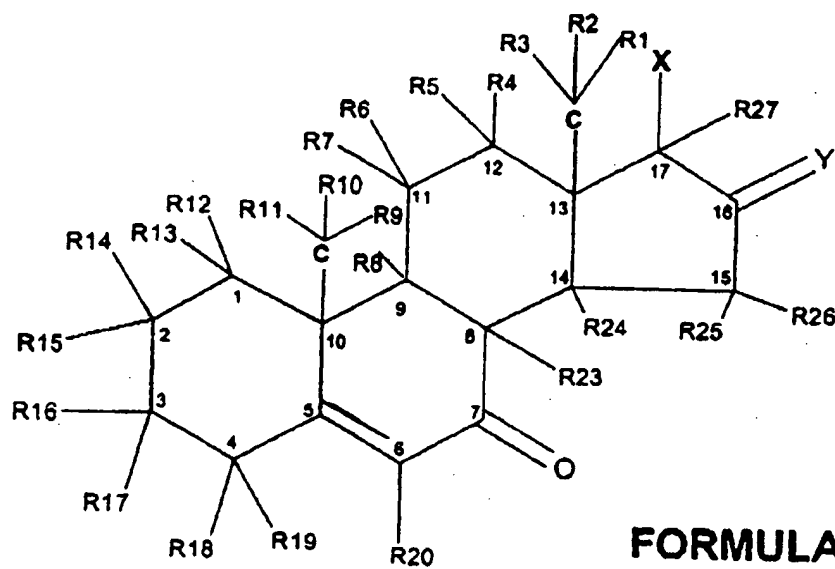


Formula 1-19









wherein:

X and Y (if present) are each independently selected from hydroxy, hydrogen, lower alkyl,  $\text{CO}_2\text{R}_{33}$  (i.e.,  $-\text{O}-\text{C}(\text{O})-\text{R}_{33}$  or  $-\text{C}(\text{O})-\text{O}-\text{R}_{33}$ ), halogen (such as Br, Cl, F or I), oxygen (double-bonded to the 16-position or 17-position carbon atom), and steroid molecule residue (residue B), wherein  $\text{R}_{33}$  is a straight or branched chain alkyl radical of 1 to 14 carbon atoms, said steroid molecule residue (residue B) having a structure corresponding to Formula I (with one hydrogen atom removed therefrom) and in which the moieties on residue B corresponding to positions X and Y (if present) are independently selected from halogen (e.g., Br, Cl, F or I), hydrogen, hydroxy, and  $\text{CO}_2\text{R}_{34}$ , wherein  $\text{R}_{34}$  is a straight or branched chain alkyl radical of 1 to 14 carbon atoms;

$\text{R}_1 - \text{R}_{16}$  and  $\text{R}_{18} - \text{R}_{31}$ , if present, are each independently selected from hydrogen, halogen (such as Br, Cl, F or I), hydroxy,  $\text{C}_1 - \text{C}_6$  alkoxy,  $\text{C}_1 - \text{C}_6$  alkyl and  $-\text{S}-\text{CN}$ ;

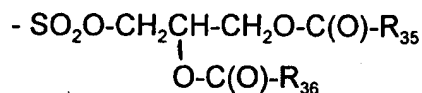
$\text{R}_{17}$  is selected from hydrogen, hydroxy, halogen (such as Br, Cl, F or I), oxygen (double-bonded to the 3-position carbon atom),  $\text{C}_1 - \text{C}_6$  alkyl,  $\text{C}_1 - \text{C}_6$  alkoxy, and  $\text{OR}_{32}$ , wherein  $\text{R}_{32}$  is selected from:

(a)  $\text{SO}_2\text{OM}$ , wherein M is selected from:

(i) hydrogen,

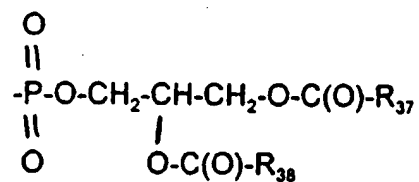
(ii) sodium,

(iii) sulphatide group having the formula:



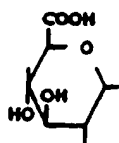
wherein  $\text{R}_{35}$  and  $\text{R}_{36}$  are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms

(iv) phosphatide group having the formula:



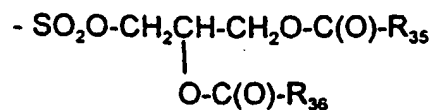
wherein  $\text{R}_{37}$  and  $\text{R}_{38}$  are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms or a glucuronide group having the formula

5



, and

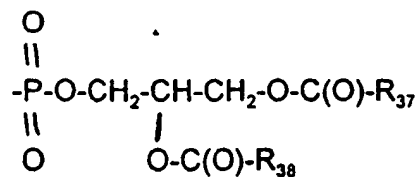
(iii) sulphatide group having the formula:



wherein  $R_{35}$  and  $R_{36}$  are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms

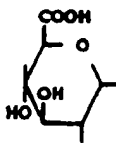
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(iv) phosphatide group having the formula:



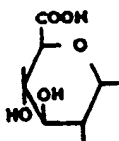
wherein  $R_{37}$  and  $R_{38}$  are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms or a glucuronide group having the formula

10

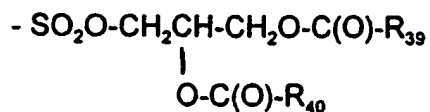


, and

(v) glucuronid group having the formula:



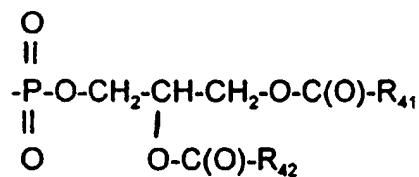
(b) sulphatide group having the formula:



5

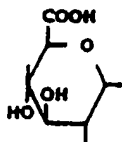
wherein  $R_{39}$  and  $R_{40}$  are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms

(c) phosphatide group having the formula:

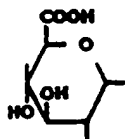


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wherein  $R_{41}$  and  $R_{42}$  are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms or a glucuronide group having the formula



(d) glucuronide group having the formula:

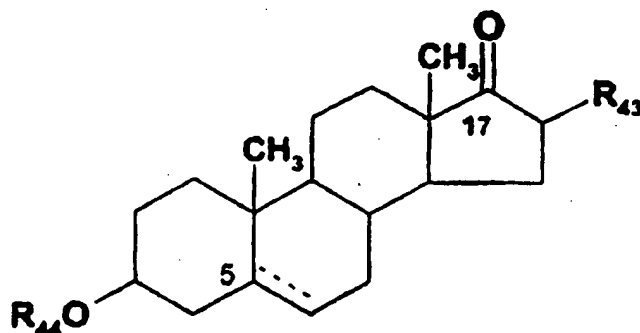


5 (e)  $C_1 - C_{18}$  fatty acid,  $C_{1-10}$  acetylenic,  $(J)_n$ -phenyl- $C_{1-5}$ -alkyl or  $(J)_n$ -phenyl- $C_{1-5}$ -alkenyl, where n is 0, 1, 2 or 3, and each J is independently selected from halogen,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkenyl,  $C_{1-4}$  alkoxy, carboxy, nitro, sulfate, sulfonyl,  $C_{1-6}$  carboxylesters or  $C_{1-6}$  sulfate esters.

10 , and metabolites, analogs and precursors thereof, and pharmaceutically acceptable salts of any such compounds, metabolites, analogs and precursors. Persons of skill in the art can readily determine whether any particular compound is such a compound, or such an analog, precursor or metabolite thereof, or pharmaceutically acceptable salt thereof.



In a preferred aspect, the anti-viral agent is selected from among compound having the following formula 1 - 25 (and precursors, metabolites and analogs ther of):

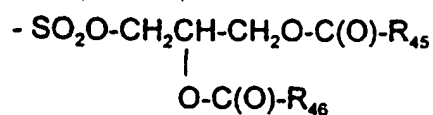


wherein

5  $R_{43}$  is a hydrogen atom or bromine atom, and

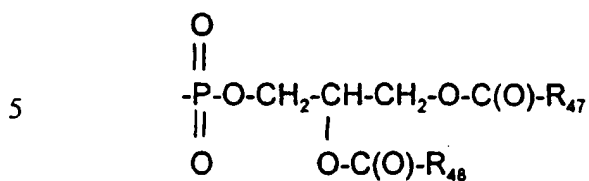
$R_{44}$  is:

- a hydrogen atom,
- an  $SO_2OM$  group (wherein M is a hydrogen atom or a sodium atom),
- a sulphatide group having the formula

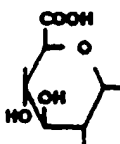


wherein  $\text{R}_{45}$  and  $\text{R}_{46}$  are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms

-a phosphatide group having the formula

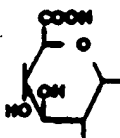


wherein  $\text{R}_{47}$  and  $\text{R}_{48}$  are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms or a glucuronide group having the formula



, or

10 -a glucuronide group having the formula



Preferably in the compound of formula 1 - 25,  $R_{43}$  and  $R_{44}$  are each hydrogen. An especially preferred compound is dehydroepiandrosterone (DHEA) wherein  $R_{43}$  and  $R_{44}$  are each hydrogen and the double bond is present. In a further embodiment of the invention, the compound is epiandrosterone wherein  $R_{43}$  and  $R_{44}$  are each hydrogen and the double bond is absent. This unsaturated 5-position steroid can also be prepared as an anti-viral agent wherein the  $R_{43}$  position is occupied by any of the following halogens (bromine, chlorine, fluorine, iodine). In a further embodiment of the invention, the compound is 16 $\alpha$ -bromoepiandrosterone, wherein  $R_{43}$  is Br,  $R_{44}$  is H and the double bond is absent. In a still further embodiment of the invention, the compound is according to formula 1 - 25, wherein  $R_{43}$  is Br,  $R_{44}$  is H and the double bond is not present (i.e., where the dotted line is shown in formula 1 - 25, there is a single bond). Other preferred compounds are dehydroepiandrosterone sulphate, wherein  $R_{43}$  is H,  $R_{44}$  is  $SO_2-OM$  and M is as hereinbefore defined and the double bond is present, and 5 $\beta$ -androstane-3 $\beta$ -ol-17-one.

As defined above, the compound of Formula 1 may also be dehydroepiandrosterone sulphatides, phosphatides, or glucuronide wherein a hydrogen atom is attached to the carbon atom at the 16-position, and  $R_{17}$  is a sulphatide, phosphatide, or glucuronide group as hereinabove defined, and the double bond between the carbon atoms at the 5-position and the 6-position is present. In particular, when  $R_{17}$  is not hydrogen, the compounds may be DHEA conjugates such as hexyl sulfate, dodecyl sulfate, octadecyl sulfate, octadecanoylglycol sulfate, O-dihexadecylglycerol sulfate, hexadecane sulfonate, dioctadecanoylglycerol phosphate, or O-hexadecylglycerol phosphate.

The compounds of Formula 1 can exist in a polymorph form.

Other preferred anti-viral agents include protease inhibitors.

Protease inhibitors are drugs that resemble pieces of the protein chain that protease normally cuts. By "gumming up" the protease "scissors," HIV protease inhibitors prevent protease from cutting long chains of proteins and enzymes into the shorter pieces that HIV needs to make new copies of itself.

New copies of HIV are still made and still push through the wall of the infected cell even if the long chains are not cut up into the correct smaller pieces. But these new copies of HIV are "defective", in that they cannot go on to infect other cells.

Protease inhibitors can greatly reduce the number of new, infectious copies of HIV made inside cells. If protease inhibitors succeed in making most new HIV viruses defective, HIV infection would not spread inside the body as quickly as it does now. The European name for protease inhibitor is proteinase inhibitor.

5 A protease inhibitor alone will generally not get rid of HIV in an infected person's body. Even though these drugs can reduce the amount of virus, more virus can remain elsewhere in the body. Because some infected cells are "dormant" or "latently infected" – meaning they are already infected but still waiting to make new virus – many researchers doubt that any one drug can remove all the virus in an infected person, believing that some virus will stay in the body in latently infected cells. Herein is described, as can be observed from bloodwork obtained according to this invention, the use of agonist to Th<sub>2</sub> cytokine, specifically IL-10, to cause viral replication. See treatment A in Figures 3(A), 3(B), 3(C) and 3(D) wherein due to viral replication, fewer latent virus are present.

15 Even so, if protease inhibitors do slow the pace at which HIV makes new copies of itself, fewer new cells would be infected by HIV, and cells already infected would eventually die. As a result, because there is less virus, fewer CD4 cells would be infected, fewer would be destroyed, and an HIV-infected person could stay healthier longer. So controlling the amount of virus would help a person fight off other infections longer and continue to live an active life.

20 The main ways protease inhibitors differ from the other anti-HIV drugs used now are in their target and in their strength. These other drugs are called reverse transcriptase inhibitors because they disturb the job of an HIV enzyme called reverse transcriptase. Reverse transcriptase is the enzyme HIV uses to change its chemical (or genetic) message into a form that can easily be inserted inside the nucleus of the infected cell.

25 This step in the HIV replication process happens soon after HIV infects a cell – much earlier than the step in which protease inhibitors are involved. Because protease inhibitors and reverse transcriptase inhibitors work at two separate steps in the HIV replication process, some studies are testing the use of drugs from both groups at the same time to treat HIV infection.

30 Protease inhibitors also differ from reverse transcriptase inhibitors in their

strength. Results from laboratory tests and tests in people show that certain protease inhibitors are many times more powerful than reverse transcriptase inhibitors in slowing the replication of HIV and in increasing the number of CD4 cells in the body.

Protease Inhibitors

|    |                             |   |
|----|-----------------------------|---|
| 5  | <u>Drug name(s)</u>         | <u>Maker</u>                                    |
|    | Invirase                    | Hoffmann-La Roche                               |
|    | (saquinavir,<br>RO-31-8959) |   |
|    | Norvir                      | Abbott  |
| 10 | (ritonavir, ABT-538)        |   |
|    | Crixivan                    | Merck   |
|    | (indinavir, MK-639)         |   |
|    | Viracept                    | Agouron   |
|    | (nelfinavir, AG-1343)       |   |
| 15 | VX-478                      | Glaxo-Wellcome/Vertex                           |
|    | 141W94                      |   |
|    | KNI-272                     | Nikko Kyoto                                     |
|    | (kynostatin)                | Pharmaceutical and National Cancer<br>Institute |
| 20 | U-103373                    | Upjohn  |
|    | CGP-53437                   | Ciba-Geigy                                      |
|    | Hoe/Bay-793                 | Hoechst-Bayer                                   |
|    | SR-41476                    | Sanofi  |

HIV can become resistant to two or more drugs at the same time. When it does, HIV is said to be cross-resistant to those drugs. Researchers studying the protease inhibitor indinavir found that HIV in some people first became resistant to the drug and then became resistant to several other protease inhibitors when they were tested later.

Other preferred anti-viral agents include reverse transcriptase inhibitors.

In the United States, physicians may prescribe five reverse transcriptase inhibitors. The common names of these drugs are:

AZT (Retrovir, zidovudine)

ddl (Videx, didanosine)

ddC (Hivid, zalcitabine)

d4T (Zerit, stavudine)

3TC (Epivir, Lamivudine)

5 In preferred embodiments of the present invention, there are provided compositions which include one or more Interleukin-4 receptor. Additionally, preferred embodiments of the present invention relate to a combination therapy for the treatment of viral infection containing (a) an Interleukin-4 receptor in combination with (b) an anti-viral agent.

10 Interleukin-4 (IL-4, also known as B-cell stimulating factor, or BSF-1) was originally characterised by its ability to stimulate the proliferation of B-cells in response to low concentrations of antibodies directed to surface immunoglobulin. More recently, IL-4 has been shown to possess a far broader spectrum of biological activities, including growth co-stimulation of T-cells, mast cells, granulocytes, megakaryocytes, and erythrocytes. In addition, IL-4 stimulates the proliferation of several IL-2 and IL-3  
15 (Interleukin-3) dependent cell lines, induces the expression of class II major histocompatibility complex molecules on resting B-cells, and enhances the secretion of IgE and IgG1 isotypes by stimulated B-cells. Both murine and human IL-4 have been definitively characterised by recombinant DNA technology and by purification to homogeneity of the natural murine protein (Yokota et al., Proc. Natl. Acad. Sci. USA  
20 83:5894, 1986; Norma et al., Nature 319:640, 1986; and Grabstein et al., J. Exp. Med. 163:1405, 1986).

The biological activities of IL-4 are mediated by specific cell surface receptors for IL-4 which are expressed on primary cells and in vitro cell lines of mammalian origin. IL-4 binds to the receptor, which then transduces a biological signal to various immune  
25 effector cells. Purified IL-4 receptor (IL-4R) compositions will therefore be useful in diagnostic assays for IL-4 or IL-4 receptor, and in raising antibodies to IL-4 receptor for use in diagnosis or therapy. In addition, purified IL-4 receptor compositions may be used directly in therapy to bind or scavenge IL-4, providing a means for regulating the biological activities of this cytokine.

30 As used herein, the terms "IL-4 receptor" or "IL-4R" refer to proteins which bind Interleukin-4 (IL-4) molecules and, in their native configuration as intact human plasma membrane proteins, play a role in transducing the biological signal provided by IL-4 to

a cell. Intact receptor proteins generally include an extracellular region which binds to a ligand, a hydrophobic transmembrane region which causes the protein to be immobilised within the plasma membrane lipid bilayer, and a cytoplasmic or intracellular region which interacts with cytoplasmic proteins and/or chemicals to deliver a biological signal to effector cells via a cascade of chemical reactions within the cytoplasm of the cell. The hydrophobic transmembrane region and a highly charged sequence of amino acids in the cytoplasmic region immediately following the transmembrane region co-operatively function to halt transport of the IL-4 receptor across the plasma membrane.

"IL-4 receptors" are proteins having amino acid sequences which are substantially similar to the native mammalian Interleukin-4 receptor amino acid sequences disclosed in Fig. 1 (SEQ ID NO. 1) (i.e., Figs. 1A, 1B, 1C), and Fig. 2 (SEQ ID NO. 2) (i.e., Figs. 2A, 2B, 2C and 2D), or fragments thereof, and which are biologically active as defined below, in that they are capable of binding Interleukin-4 (IL-4) molecules or transducing a biological signal initiated by an IL-4 molecule binding to a cell, or cross-reacting with anti-IL-4R antibodies raised against IL-4R from natural (i.e., nonrecombinant) sources. The native human IL-4 receptor molecule has an apparent molecular weight by SDS-PAGE of about 140 kilodaltons (kDa). The native murine IL-4 receptor molecule has an apparent molecular weight by SDS-PAGE of about 140 kilodaltons (kDa). The terms "IL-4 receptor" or "IL-4R" include, but are not limited to, soluble IL-4 receptors, as defined below. Specific IL-4 receptor polypeptides are designated herein by parenthetically indicating the amino acid sequence numbers, followed by any additional amino acid sequences. As used throughout the specification, the term "mature" means a protein expressed in a form lacking a leader sequence as may be present in full-length transcripts of a native gene. Various bioequivalent protein and amino acid analogs are described in the detailed description of the invention.

"Substantially similar" IL-4 receptors include those whose amino acid or nucleic acid sequences vary from the native sequences by one or more substitutions, deletions, or additions, the net effect of which is to retain biological activity of the IL-4R protein. For example, nucleic acid subunits and analogs are "substantially similar" to the specific DNA sequences disclosed herein if: (a) the DNA sequence is derived from the coding region of a native mammalian IL-4R gene; (b) the DNA sequence is capable of

hydrodisation to DNA sequences of (a) under moderately stringent conditions and which encode biologically active IL-4R molecules; or DNA sequences which are degenerate as a result of the genetic code to the DNA sequences defined in (a) or (b) and which encode biologically active IL-4R molecules. Substantially similar analog proteins will generally be greater than about 30 percent similar to the corresponding sequence of the native IL-4R. Sequences having lesser degrees of similarity but comparable biological activity are considered to be equivalents. More preferably, the analog protein will be greater than about 70 percent similar to the corresponding sequence of the native IL-4R, in which case they are defined as being "substantially identical". In defining nucleic acid sequences, all subject nucleic acid sequences capable of encoding substantially similar amino acid sequences are considered substantially similar to a reference nucleic acid sequence. Percent similarity may be determined, for example, by comparing sequence information using the GAP computer program, version 6.0, available from the University of Wisconsin Genetics Computer Group (UWGCG). The GAP program utilises the alignment method of Needleman and Wunsch (J. Mol. Biol. 48: 443, 1970), as revised by Smith and Waterman (Adv. Appl Math. 2:482, 1981). Briefly, the GAP program defines similarity as the number of aligned symbols (i.e., nucleotides or amino acids) which are similar, divided by the total number of symbols in the shorter of the two sequences. The preferred default parameters for the GAP program include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) for nucleotides, and the weighted comparison matrix of Gribskov and Burgess, Nucl. Acids Res. 14:6745, 1986, as described by Schwartz and Dayhoff, ed., Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, pp. 353-358, 1979; (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

"Soluble IL-4 receptor" or "sIL4-R" as used in the context of the present invention refers to a protein, or a substantially equivalent analog, having an amino acid sequence corresponding to the extracellular region of native IL-4 receptors, for example, polypeptides having the amino acid sequences substantially equivalent to the sequences of amino acids 1-208 of Fig. 1A (part of SEQ ID NO. 1), amino acids 1-207 of Fig. 2A (part of SEQ ID NO. 2). Equivalent sIL-4Rs include polypeptides which vary



from the sequences shown in Figs. 1 or 2 (SEQ ID NOS. 1 and 2) by one or more substitutions, deletions, or additions, and which retain the ability to bind IL-4 and inhibit the ability of IL-4 to transduce a signal via cell surface bound IL-4 receptor proteins. Because sIL-4R proteins are devoid of a transmembrane region, they are secreted from the host cell in which they are produced. When administered in therapeutic formulations, sIL-4R proteins circulate in the body and bind to circulating IL-4 molecules, preventing interaction of IL-4 with natural IL-4 receptors and inhibiting transduction of IL-4 mediated biological signals, such as immune or inflammatory responses. The ability of a polypeptide to inhibit IL-4 signal transduction can be determined by transfecting cells with recombinant IL-4 receptor DNAs to obtain recombinant receptor expression. The cells are then contacted with IL-4 and the resulting metabolic effects examined. If an effect results which is attributable to the action of the ligand, then the recombinant receptor has signal transducing activity. Exemplary procedures for determining whether a polypeptide has signal transducing activity are disclosed by Idzerda et al., J. Exp. Med., March 1990 in press, Curtis et al., Proc. Natl. Acad. Sci. USA 86: 3045 (1989), Prywes et al., EMBO J. 5:2179 (1986) and Chou et al., J. Biol. Chem. 262:1842 (1987). Alternatively, primary cells of cell lines which express an endogenous IL-4 receptor and have a detectable biological response to IL-4 could also be utilised. Such is the case with the CTLL-2 cell line which responds by short term proliferation in response to either IL-2 or IL-4; the IL-4 induced proliferation can be blocked specifically by the addition of exogenous soluble IL-4R (Mosley et al., Cell 59:335 (1989). In addition, any one of the in vivo or in vitro assays described in Examples 1-10 can be utilised to determine whether a soluble IL-4R inhibits transduction of a specific IL-4 mediated biological signal. The cloning, sequencing and expression of full-length and soluble forms of the receptor for murine IL-4 have recently been described by Mosley et al., Cell 59:335, 1989.

"Recombinant," as used herein, means that a protein is derived from recombinant (e.g., microbial or mammalian) expression systems. "Microbial" refers to recombinant proteins made in bacterial or fungal (e.g., yeast) expression systems. As a product, "recombinant microbial" defines a protein produced in a microbial expression system which is essentially free of native endogenous substances. Protein expressed in most bacterial cultures, e.g., E. coli, will be free of glycan. Protein expressed in yeast

may have a glycosylation pattern different from that expressed in mammalian cells.

“Biologically active,” as used throughout the specification, e.g., as a characteristic of IL-4 receptors, means that a particular molecule shares sufficient amino acid sequence similarity with the embodiments of the present invention disclosed herein to be capable of binding detectable quantities of IL-4, transducing an IL-4 signal to a cell, for example, as a component of a hybrid receptor construct, or cross-reacting with anti-IL-4R antibodies raised against IL-4R from natural (i.e., nonrecombinant) sources. Preferably, biologically active IL-4 receptors within the scope of the present invention are capable of binding greater than 0.1 nmoles IL-4 per nmole receptor, and most preferably, greater than 0.5 nmole IL-4 per nmole receptor in standard binding assays (see below).

“DNA sequence” refers to a DNA molecule, in the form of a separate fragment or as a component of a larger DNA construct, which has been derived from DNA isolated at least once in substantially pure form, i.e., free of contaminating endogenous materials and in a quantity or concentration enabling identification, manipulation, and recovery of the sequence and its component nucleotide sequences by standard biochemical methods, for example, using a cloning vector. Such sequences are preferably provided in the form of an open reading frame uninterrupted by internal nontranslated sequences, or introns, which are typically present in eukaryotic genes. Genomic DNA containing the relevant sequences could also be used. Sequences of non-translated DNA may be present 5' or 3' from the open reading frame, where the same do not interfere with manipulation or expression of the coding regions.

“Nucleotide sequence” refers to a heteropolymer of deoxyribonucleotides. DNA sequences encoding the proteins provided by this invention can be assembled from cDNA fragments and short oligonucleotide linkers, or from a series of oligonucleotides, to provide a synthetic gene which is capable of being expressed in a recombinant transcriptional unit.

“Recombinant expression vector” refers to a replicable DNA construct used either to amplify or to express DNA which encodes IL-4R and which includes a transcriptional unit comprising an assembly of (1) a genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers, (2) a structural or coding sequence which is transcribed into mRNA and translated into

protein, and (3) appropriate transcription and translation initiation and termination sequences. Structural elements intended for use in yeast expression systems preferably include a leader sequence enabling extracellular secretion of translated protein by a host cell. Alternatively, where recombinant protein is expressed without a leader or transport sequence, it may include an N-terminal methionine residue. This residue may optionally be subsequently cleaved from the expressed recombinant protein to provide a final product.

"Recombinant microbial expression system" means a substantially homogenous monoculture of suitable host micro-organisms, for example, bacteria such as *E. coli* or yeast such as *S. cerevisiae*, which have stably integrated a recombinant transcriptional unit into chromosomal DNA or carry the recombinant transcriptional unit as a component of a resident plasmid. Generally, cells constituting the system are the progeny of a single ancestral transformant. Recombinant expression systems as defined herein will express heterologous protein upon induction of the regulatory elements linked to the DNA sequence or synthetic gene to be expressed.

The present invention provides substantially homogeneous recombinant mammalian IL-4R polypeptides substantially free of contaminating endogenous materials and, optionally, without associated native-pattern glycosylation. The native murine and human IL-4 receptor molecules are recovered from cell lysates as glycoproteins having an apparent molecular weight by SDS-PAGE about 130-145 kilodaltons (kDa). Mammalian IL-4R of the present invention include, by way of example, primate, human, murine, canine, feline, bovine, ovine, equine and porcine IL-4R. Derivatives of IL-4R within the scope of the invention also include various structural forms of the primary protein which retain biological activity. Due to the presence of ionisable amino and carboxyl groups, for example, an IL-4R protein may be in the form of acidic or basic salts, or in neutral form. Individual amino acid residues may also be modified by oxidation or reduction.

The primary amino acid structure may be modified by forming covalent or aggregative conjugates with other chemical moieties, such as glycosyl groups, lipids, phosphate, acetyl groups and the like, or by creating amino acid sequence mutants. Covalent derivatives are prepared by linking particular functional groups to IL-4R amino acid side chains or at the N- or C-termini. Other derivatives of IL-4R within the scope

of this invention include covalent or aggregative conjugates of IL-4R or its fragments with other proteins or polypeptides, such as by synthesis in recombinant culture as N-terminal or C-terminal fusions. For example, the conjugated peptide may be a signal (or leader) polypeptide sequence at the N-terminal region of the protein which co-translationally or post-translationally directs transfer of the protein from its site of synthesis to its site of function inside or outside of the cell membrane or wall (e.g., the G-factor leader). IL-4R protein fusions can comprise peptides added to facilitate purification or identification of IL-4R (e.g., poly-His). Specific examples of a poly-HIS fusion construct that is biologically active are soluble human IL-4R (1-207) His His and soluble human IL-4R (1-207) His His His His His His (SEQ ID NO. 3). The amino acid sequence of IL-4 receptor can also be linked to the peptide Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys (DYKDDDDK) (SEQ ID NO. 4) (Hopp et al., Bio/Technology 6:1204, 1988). The latter sequence is highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody, enabling rapid assay and facile purification of expressed recombinant protein. This sequence is also specifically cleaved by bovine mucosal enterokinase at the residue immediately following the Asp-Lys pairing. Fusion proteins capped with this peptide may also be resistant to intracellular degradation in *E. coli*. A specific example of such a peptide is soluble human IL-4R (1-207) Asp Tyr Lys Asp Asp Asp Asp Lys (SEQ ID NO. 3).

IL-4R derivatives may also be used as immunogens, reagents in receptor-based immunoassay, or as binding agents for affinity purification procedures of IL-4 or other binding ligands. IL-4R derivatives may also be obtained by cross-linking agents, such as M-maleimidobenzoyl succinimide ester and N-hydroxysuccinimide, at cysteine and lysine residues. IL-4R proteins may also be covalently bound through reactive side groups to various insoluble substrates, such as cyanogen bromide-activated, bisoxirane-activated, carbonyldiimidazole-activated or tosyl-activated agarose structures, or by adsorbing to polyolefin surfaces (with or without glutaraldehyde cross-linking). Once bound to a substrate, IL-4R may be used to selectively bind (for purposes of assay or purification) anti-IL-4R antibodies or IL-4.

The present invention also includes IL-4R with or without associated native-pattern glycosylation. IL-4R expressed in yeast or mammalian expression systems, e.g., COS-7 cells, may be similar or significantly different in molecular weight and

glycosylation pattern than the native molecules, depending upon the expression system. Expression of IL-4R DNAs in bacteria such as *E. coli* provides non-glycosylated molecules. Functional mutant analogs of mammalian IL-4R having inactivated N-glycosylation sites can be produced by oligonucleotide synthesis and ligation or by site-specific mutagenesis techniques. These analog proteins can be produced in a homogenous, reduced-carbohydrate form in good yield using yeast expression systems. N-glycosylation sites in eukaryotic proteins are characterised by the amino acid triplet Asn-A<sub>1</sub>-Z, where A<sub>1</sub> is any amino acid except Pro, and Z is Ser or Thr. In this sequence, asparagine provides a side chain amino group for covalent attachment of carbohydrate. Such a site can be eliminated by substituting another amino acid for Asn or for residue Z, deleting Asn or Z, or inserting a non-Z amino acid between A<sub>1</sub> and Z, or an amino acid other than Asn between Asn and A<sub>1</sub>.

IL-4R derivatives may also be obtained by mutations of IL-4R or its subunits. An IL-4R mutant, as referred to herein, is a polypeptide homologous to IL-4R but which has an amino acid sequence different from native IL-4R because of a deletion, insertion or substitution. Like most mammalian genes, mammalian IL-4 receptors are presumably encoded by multi-exon genes. Alternative mRNA constructs which can be attributed to different mRNA splicing events following transcription, and which share large regions of identity or similarity with the cDNAs claimed herein, are considered to be within the scope of the present invention.

Bioequivalent analogs of IL-4R proteins may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues can be deleted or replaced with other amino acids to prevent formation of incorrect intramolecular disulfide bridges upon renaturation. Other approaches to mutagenesis involve modification of adjacent diacidic amino acid residues to enhance expression in yeast systems in which KEX2 protease activity is present. Generally, substitutions should be made conservatively; i.e., the most preferred substitute amino acids are those having physiochemical characteristics resembling those of the residue to be replaced. Similarly, when a deletion or insertion strategy is adopted, the potential effect of the deletion or insertion on biological activity should be considered.

Subunits of IL-4R may be constructed by deleting terminal or internal residues

or sequences. Particularly preferred subunits include those in which the transmembrane region and intracellular domain of IL-4R are deleted or substituted with hydrophilic residues to facilitate secretion of the receptor into the cell culture medium. The resulting protein is a soluble IL-4R molecule which may retain its ability to bind IL-4.

5 Particular examples of soluble IL-4R include polypeptides having substantial identity to soluble murine IL-4R (1-208), soluble human IL-4R (1-207) and soluble human IL-4R (1-198), all of which retain the biological activity of soluble human IL-4R (1-207). Chimeric polypeptides comprising fragments of human and murine IL-4R may also be constructed, for example, IL-4R (1-197) Pro Ser Asn Glu Asn Leu (SEQ ID NO. 5),

10 which is comprised of the sequence of amino acids 1-197 of human IL-4R followed by the N-terminal six amino acids of soluble murine IL-4R clone 18. This polypeptide has been found to retain the biological activity of soluble IL-4R (1-207).

To prepare pharmaceutical compositions including the peptide IL-4R the peptide is admixed with a pharmaceutically acceptable carrier or excipient which is preferably

15 inert. Preparation of such pharmaceutical compositions are known in the art: see, for example, Remington's Pharmaceutical Sciences and U.S. Pharmacopeia: National Formulary, Mack Publishing Company, Easton, Pa. (1984).

The peptide may be administered in aqueous vehicles such as water, saline or buffered vehicles with or without various additives and/or diluting agents. A suspension,

20 such as a zinc suspension, can be prepared to include the peptide. Such a suspension can be useful for subcutaneous (SQ) or intramuscular (IM) injection. By adjusting the proportion of zinc and the acidity, the absorption rate of the peptide can be manipulated.

The proportion of peptide and additive can be varied over a broad range so long

25 as both are present in effective amounts. On a per-dose basis, the amount of the peptide can range from about 10 µg to about 1500 µg of each protein per kilogram body weight of the patients. A preferable range is from about 300 µg to about 800 µg.

Compositions may be ingested orally or injected into the body. Injections are usually intramuscular, subcutaneous, intradermal or intravenous. Alternatively, intra-

30 articular injection or other routes could be used in appropriate circumstances. Additionally, compositions including the peptide IL-4R may be implanted into a patient or injected using a drug delivery system. See, for example, Urquhart, et al., Ann. Rev.

Pharmacol. Toxicol. 24: 199-236 (1984); Lewis, ed. "Controlled Release of Pesticides and Pharmaceuticals" (Plenum Press, New York, 1981); U.S. Pat. No. 3,773,919; and U.S. Pat. No. 3,270,960.

5 Preferably, the peptide is administered parenterally and preferably in a unit dosage injectable form. Examples of an injectable form include solutions, suspensions and emulsions. Typically, the peptide is injected in association with a pharmaceutical carrier such as normal saline, Ringer's solution, dextrose solution and other aqueous carriers known in the art. Appropriate non-aqueous carriers may also be used and examples include fixed oils and ethyl oleate. A preferred carrier is 5% dextrose in  
10 saline. Frequently, it is desirable to include additives in the carrier such as buffers and preservatives or other substances to enhance isotonicity and chemical stability.

Preferably, the peptide, IL-4R is formulated in purified form substantially free of aggregates and other proteins at a concentration of about 1 to 30 mg/ml. The concentration of the peptide in a unit dose is from about 60 micrograms to 200  
15 milligrams varying with the application and the potency of the peptide. Although IL-4R may be administered by any of a number of routes, an intravenous infusion or bolus is preferred. Most preferably, an intravenous injection delivers about 1 mg to about 100 mg of the peptide per day. The dose range is about 15 µg to 1500 µg per kilogram of body weight of the recipient per day per peptide. Dosages should be varied according  
20 to side effects and blood cell counts which should be monitored frequently, preferably daily.

The agonist and antagonists are preferably administered intravenously. A preferred antagonist is an antibody specific for binding to IL-4. The antibodies can be chimeric, recombinant, polyclonal or monoclonal. Autologous antibodies, human or  
25 humanized antibodies are preferred for safety when human patients are being treated. The preferred single dosage of antibodies is 1-10 mg/kg body weight per antibody. Alternatively, the amount of the antibody administered in a single dose is about 10 to about 100 µg per milliliter of patient sera.

30 An effective amount for a particular patient may vary depending on factors such as the condition being treated, the overall health of the patient, the method route and dose of administration and the severity of side effects. Determination of the appropriate dose is made by the clinician using parameters known in the art. Generally, the dose

begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achieved.

The total daily dose of the peptide can be given as bolus injection, such as an intravenous injection, or it can be given as a continuous infusion. Alternatively, the daily dosage may be divided into several smaller doses for multiple bolus intravenous administration. Other routes of administration such as intramuscular injection, can be employed.

In one aspect of the invention, there is provided a method which comprises co-administering to the mammal an effective amount of each of agonist or antagonist to IL-4 and one or more anti-viral agents. The mammal is preferably a human. The co-administering can be simultaneous or sequential. Generally, "co-administering" means that the cytokine is present in the recipient during a specified time interval. Typically, the anti-viral agent is administered within the half life of the cytokine. Preferably, the co-administration is parenteral, and most preferably it is intravenous. The effective amount is selected from a range from about 15 µg to about 1500 µg per kilogram of body weight of the mammal.

Mutations in nucleotide sequences constructed for expression of analog IL-4Rs must, of course, preserve the reading frame phase of the coding sequences and preferably will not create complementary regions that could hybridise to produce secondary mRNA structures, such as loops or hairpins, which would adversely affect translation of the receptor mRNA. Although a mutation site may be predetermined, it is not necessary that the nature of the mutation per se be predetermined. For example, in order to select for optimum characteristics of mutants at a given site, random mutagenesis may be conducted at the target codon and the expressed IL-4R mutants screened for the desired activity.

This invention includes (among others) treatments against viral, bacterial, and mycoplasma infections by any suitable route including enteric, parenteral, topical, oral, rectal, nasal or vaginal routes. Parenteral routes include subcutaneous, intramuscular, intravenous and sublingual administration. The preferred route of administration would be an intravenous one but this may not be feasible with a large patient base and oral administration of compounds may be the most preferred route.

The Antagonists are preferably administered intravenously. A preferred



antagonist is an antibody specific for binding to IL-4. The antibodies can be chimeric, recombinant, polyclonal or monoclonal. Autologous antibodies, human or humanized antibodies are preferred for safety when human patients are being treated. The preferred single dosage of antibodies is 1-10 mg/kg body weight per antibody. Alternatively, the amount of the antibody administered in a single dose is about 10 to about 100 µg per milliliter of patient sera.

#### Patient Treatment

The patient was HIV+ and had been taking a combination course of both reverse transcriptase inhibitors combined with Protease inhibitors. His viral load had decreased initially upon the commencement of the Protease and Reverse transcriptase inhibitors combination therapy regime. However, his CD4 absolute and percentage values did not show any improvement with this conventional therapy. See Figs. 3A, 3B, 3C and 3D wherein the patient was monitored over a period of 208 days during which he was receiving various therapies as per the present invention. Treatment A, herein the patient stopped all his standard therapy and was administered Anti-serum to IL-10 (Recombinant Human). During this period viral reproduction was observed. Over a period of 14 days, the HIV-I RNA g PCR rose from 15,384 to 157,812. The bloodwork analysis obtained by the administration of a Th<sub>2</sub> cytokine antibody alone (no anti viral treatment) is contrary to the teaching of International Publication Number WO 94/06473. The patient was maintained on his original conventional (Protease and Reverse transcriptase inhibitors) therapy but he was also co-administered rabbit generated polyclonal Antiserum to human Interleukin 10 and human Interleukin 4, treatment B Figs. 3A, 3B, 3C and 3D. The antibody class was IgG and the respective antigens were recombinant human IL-10 and recombinant human IL-4 (see Tables A and B, below).

---

TABLE A

|    |                         |   |
|----|-------------------------|---|
|    | DESCRIPTION:            | Anti-serum to recombinant human IL-10   |
|    | FORM:                   | Liquid  |
|    | RECOMMENDED DILUENT:    | Tris Buffered Saline  |
| 5  | CONCENTRATION:          | 0.65 mg/ml  |
|    | STABILIZERS:            | none  |
|    | PRESERVATIVE:           | none  |
|    | STERILITY:              | Sterile filtered (0.2um)  |
|    | HOST SPECIES:           | Rabbit  |
| 10 | ANTIBODY CLASS:         | IgG   |
|    | ANTIGEN USED:           | Recombinant human IL-10   |
|    | METHOD OF PURIFICATION: | Ion exchange chromatography   |
|    | METHOD OF QUANTITATION: | Pierce BCA Protein Assay  |
|    | SPECIFICITY:            | Human IL-10   |
| 15 | CROSS-REACTIVITY:       | No cross reactivity with WHO standards: IL-1-alpha, IL-1-beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-11, IL-15, EGF, FGFa, FGFb, GM-CSF, GRO-alpha, IGF-1, IGF-11, IFN-alpha, IFN-gamma, MIP-1-alpha, MIP-1-beta, MCAF, MCP-2, MCP-3, PDGF-aa, RANTES, TGF-alpha, TNF-alpha, TNF-beta, TPO, VEGF, murine IL-1-alpha, murine IL-1-beta, and IgG done by |
| 20 |                         | EIA.  |
|    | SPECIES TESTED:         | Human by EIA  |
|    | MINIMUM DILUTION:       | 1:100   |
|    | STORAGE:                | Short term 4°C and -20°C for long term  |

TABLE B

|    |                           |   |
|----|---------------------------|---|
|    | DESCRIPTION:              | Anti-serum to recombinant human IL-4  |
|    | SPECIFICITY:              | Human IL-4  |
|    | PRODUCT FORM:             | Liquid  |
| 5  | RECOMMENDED DILUENT:      | Tris Buffered Saline  |
|    | STABILIZERS:              | none  |
|    | PRESERVATIVES:            | none  |
|    | ANTIBODY CLASS:           | IgG   |
|    | CONCENTRATION:            | 2.14mg/ml   |
| 10 | ANTIGEN USED TO GENERATE: | Recombinant human IL-4  |
|    | PURIFICATION:             |   |
|    | Method of purification:   | Ion exchange chromatography   |
|    | Method of quantitation:   | Pierce BCA Protein Assay  |
|    | CROSS-REACTIVITY:         | No cross reactivity with WHO standards:   |
| 15 |                           | IL-1-alpha, IL-1-beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-11, IL-13, IL-15, EGF, FGFa, FGFb, GM-CSF, GRO-alpha, IGF-1, IGF-11, IFN-alpha, IFN-gamma, MIP-1-alpha, MIP-1-beta, MCAF, MCP-2, MCP-3, PDGF-aa, RANTES, TGF-alpha, TNF-alpha, TNF-beta, TPO, VEGF, murine IL-1-alpha, murine IL-1-beta, and IgG done by EIA |
| 20 | MINIMUM DILUTION:         | 1:100   |
|    | STORAGE:                  | Short term 2-8°C long term at -20°C   |

The dosage used was 2 mg/ml of each antibody and 2 mls was administered IV every day for seven days. The results were that viral load as measured by PCR decreased by one log the first week of the injections and to undetectable levels by the following week (14 days < 400 copies). The Helper T (CD4) absolute and percentage readings changed from 177 (wk. 0) to 276 (wk. 1) and from 11% (wk.0) to 15% (wk. 1). There was a simultaneous decrease in suppresser T(CD8) percentage from 73% (wk.0) to 67% (wk.1). The patient experienced some flu-like symptoms immediately following the injections but no toxicity or discomfort were reported for this therapy. The patient showed a rapid development of anti-rabbit antibodies and further therapy required the

use of monoclonal Antibodies utilize the human receptor (recombinant) to either one or both of Interleukin-4 or Interleukin-10. This cytokine removal therapy has demonstrated a dramatic ability to augment conventional combination anti-viral therapy and to rapidly lower viral load levels so that fewer viruses have long term exposure to the anti-viral drugs to allow resistant strain development. Also from our analysis of HIV viral strain removal it would appear from the viral isolates present before and after this cytokine antibody therapy that Protease and R. T. resistant strains were cleared by the patient's immune system similar to naïve strains. Treatment C relates to a period when the patient maintained his conventional therapy and was administered only anti-serum to IL-10. From other HIV patient studies which utilized the similar administration of the antibodies to recombinant human Interleukin 4 and/or Interleukin 10 it was demonstrated that whilst the co-administration of conventional anti-viral drugs that the removal of these cytokines (IL-4/IL-10) without the presence of concurrent anti-viral drugs to suppress viral replication that a 3 log increase in PCR viral levels occurred within 2 weeks of antibody therapy.

## CLAIMS

1. A method of enhancing immune response in a patient, said method comprising a combination therapy containing one or more anti-viral agent and one or more agonist and/or Antagonist to a Th<sub>2</sub> cytokine.
- 5 2. A method of treating a viral infection in a mammal, human or animal, said method comprising a combination therapy containing one or more anti-viral agent and one or more agonist and/or Antagonist to a Th<sub>2</sub> cytokine.
3. A method of treating a condition in a mammal, human or animal, said method comprising a combination therapy containing one or more anti-viral agent and one or  
10 more agonist and/or Antagonist to a Th<sub>2</sub> cytokine.
4. A pharmaceutical formulation containing one or more anti-viral agent and one or more agonist and/or Antagonist to a Th<sub>2</sub> cytokine.
5. A method of administration to a patient a pharmaceutical formulation containing one or more anti-viral agent and one or more agonist and/or antagonist to  
15 a Th<sub>2</sub> cytokine.
6. A method of providing an immunosuppressive or immunoregulatory effect in a mammal, human or animal, comprising a combination therapy containing one or more anti-viral agent and Agonist and/or Antagonist to a Th<sub>2</sub> cytokine.
7. A combination therapy comprising the administration to a patient one or more  
20 anti-viral agents and one or more agonist and/or Antagonist to a Th<sub>2</sub> cytokine.
8. A method of enhancing immune response in a patient, said method comprising a combination therapy containing a protease inhibitor and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.
9. A method of treating a viral infection in a mammal, human or animal, said  
25 method comprising a combination therapy containing a protease inhibitor and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.
10. A method of treating a condition in a mammal, human or animal, said method comprising a combination therapy containing a protease inhibitor and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.
- 30 11. A pharmaceutical formulation containing a protease inhibitor and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

12. A method of administration to a patient a pharmaceutical formulation containing a protease inhibitor and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

13. A method of providing an immunosuppressive or immunoregulatory effect in a mammal, human or animal, comprising a combination therapy containing a protease inhibitor and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

14. A combination therapy comprising the administration to a patient a protease inhibitor and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

15. A method of enhancing immune response in a patient, said method comprising a combination therapy containing a reverse transcriptase inhibitor and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

16. A method of treating a viral infection in a mammal, human or animal, said method comprising a combination therapy containing a reverse transcriptase inhibitor and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

17. A method of treating a condition in a mammal, human or animal, said method comprising a combination therapy containing a reverse transcriptase inhibitor and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

18. A pharmaceutical formulation containing a reverse transcriptase inhibitor and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

19. A method of administration to a patient a pharmaceutical formulation containing a reverse transcriptase inhibitor and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

20. A method of providing an immunosuppressive or immunoregulatory effect in a mammal, human or animal, comprising a combination therapy containing reverse transcriptase inhibitor and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

21. A combination therapy comprising the administration to a patient a protease inhibitor and a receptor to Interleukin-4.

22. A method of enhancing immune response in a patient, said method comprising administering an amount of a receptor to Interleukin-4 in combination with one or more protease inhibitors.

23. A method of treating a viral infection in a mammal, human or animal, said method comprising administering an amount of receptor to Interleukin-4 in combination

with one or more protease inhibitors.

24. A method of treating a condition in a mammal, human or animal, said method comprising administering an amount of receptor to Interleukin-4 in combination with one or more protease inhibitors.

5        25. A pharmaceutical formulation containing a receptor to Interleukin-4 in combination with one or more protease inhibitors.

26. A method of administration to a patient a pharmaceutical formulation containing a receptor to Interleukin-4 in combination with one or more protease inhibitors.

10       27. A method of providing an immunosuppressive or immunoregulatory effect in a mammal, human or animal, comprising administering to said mammal a receptor to Interleukin-4 in combination with one or more protease inhibitors.

28. A combination therapy according to any one of claims 1, 2, 3, 6 - 10, 13 - 17, 21, 22, 43 - 45, and 48 - 51, wherein each component of the combination is  
15 administered jointly or at different stages of a treatment regimen.

29. A Th<sub>2</sub> cytokine according to any one of claims 1 - 21 and 43 - 50, wherein the cytokine is one or more of the following: Interleukin-3, Interleukin-4, Interleukin-5, Interleukin-6, Interleukin-9, Interleukin-10, Interleukin-13 and Cytokine GM-CSF.

30. A method according to any one of claims 1, 3, 5, 10 - 12, 15, 16, 19 - 21, 24, 25, 27, 45, 46, 47, 50, 53, 54 and 56, wherein the mammal or patient has a neoplastic  
20 condition.

31. A protease inhibitor according to claim 8,9,10,11,12, 13,14,21,22,23,24,25,26 & 27 wherein the Protease Inhibitor may be one or more of the following Inviase (saquinavir, RO-31-8959) Hoffmann-La Roche. Norvir (ritonavir, ABT-538, Abbott. Crixivan (indinavir, MK-639), Agouron Viracept (nelfinavir, AG-1343) Agouron. VX-478  
25 141w94 Glaxo-Wellcome/Vertex, KNI-272 (kynostatin), Nikko Kyoto, Pharmaceutical and National Cancer Institute. U-103373, Upjohn. CGP-53437, Ciba-Geigy. Hoe/Bay-793, Hoechst-Bayer. SR-41476, Sanofi.

32. A reverse transcriptase inhibitor according to claims 15-20 inclusive wherein  
30 the inhibitor may be one or more of the following AZT (Retrovir, zidovudine), ddI (Videx, didanosine), ddC (Hivid, zalcitabine), d4T (Zerit, stavudine), 3TC (Epivir, Lamivudine).

33. Agonist and/or antagonist according to any one of claims 1 - 21 and 43 - 50, wherein the agonist and/or antagonist is an antibody specific to a Th<sub>2</sub> cytokine, wherein the antibodies are chimeric, recombinant, polyclonal, monoclonal or antibodies of plant origin.

5 34. Agonist and/or antagonist according to any one of claims 1 - 21 and 43 - 50, wherein the agonist and/or antagonist is a receptor or mutein receptor to specific Th<sub>2</sub> cytokines.

35. A method of enhancing viral replication in a patient, said method comprising a pharmaceutical formulation containing an agonist and/or antagonist to a Th<sub>2</sub> cytokine.

10 36. A method according to claim 35, wherein the cytokine is at least one member of the group consisting of IL-4, IL-5, IL-6, IL-10 and IL-13.

37. A method according to claim 35 or 36, wherein the Th<sub>2</sub> cytokine is selected from the group consisting of IL-4, IL-5, IL-6, IL-10 and IL-13.

15 38. A method according to any one of claims 22 - 27 and 51 - 56, wherein the receptor to the cytokines is administered by IV, enema or transdermal patch in dose amounts of between 10 and 1000 micrograms per day.

39. A method according to any one of claims 22 - 27 and 51 - 56, wherein the receptor to the cytokines is administered as a soluble receptor.

20 40. A combination therapy according to any one of claims 1 - 3, 6, 8, 9, 10, 13 - 17, 20, 21, 28, 43 - 45, and 48 - 50, wherein the combination therapy is sequentially co-administered.

41. A combination therapy according to any one of claims 1 - 3, 6, 8, 9, 10, 13 - 17, 20, 21, 28, 43 - 45 and 48 - 50, wherein the combination therapy is parenterally co-administered.

25 42. A combination therapy according to any one of claims 1-3,6,8,9,10, 13-17,20,21,28,43-45 and 48-50, wherein the combination therapy is intravenously co-administered.

30 43. A method of enhancing immune response in a patient, said method comprising a combination therapy containing a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.



44. A method of treating a viral infection in a mammal, human or animal, said method comprising a combination therapy containing a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

45. A method of treating a condition in a mammal, human or animal, said method comprising a combination therapy containing a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

46. A pharmaceutical formulation containing a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

47. A method of administration to a patient a pharmaceutical formulation containing a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

48. A method of providing an immunosuppressive or immunoregulatory effect in a mammal, human or animal, comprising a combination therapy containing a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

49. A combination therapy comprising the administration to a patient a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th<sub>2</sub> cytokine.

50. A combination therapy comprising the administration to a patient of a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and a receptor to Interleukin-4.

51. A method of enhancing immune response in a patient, said method comprising administering an amount of a receptor to Interleukin-4 in combination with one or more compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor.

52. A method of treating a viral infection in a mammal, human or animal, said method comprising administering an amount of receptor to Interleukin-4 in combination with one or more compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor.

53. A method of treating a condition in a mammal, human or animal, said method comprising administering an amount of receptor to Interleukin-4 in combination with one or more compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor.

54. A pharmaceutical formulation containing a receptor to Interleukin-4 in combination with one or more compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor.

55. A method of administration to a patient a pharmaceutical formulation containing a receptor to Interleukin-4 in combination with one or more compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor.

56. A method of providing an immunosuppressive or immunoregulatory effect in a mammal, human or animal, comprising administering to said mammal a receptor to Interleukin-4 in combination with one or more compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor.

57. A method of enhancing immune response in a patient in need of such enhancement, comprising administering to said patient (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine.

58. A method of treating viral infection, bacterial infection, fungal infection, parasitic infection and/or infectious protein units in a patient in need of such treatment, or minimizing the likelihood of such infection and/or reducing the potential future adversity of such infection in a patient, comprising administering to said patient (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine.

59. A method of providing immunosuppression or immunoregulatory effect in patient in need such effect, comprising administering to said patient (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine.

60. A method as recited in any one of claims 57-59, wherein said patient is a mammal.

61. A method as recited in any one of claims 57-60, wherein said viral infection is a retroviral infection.

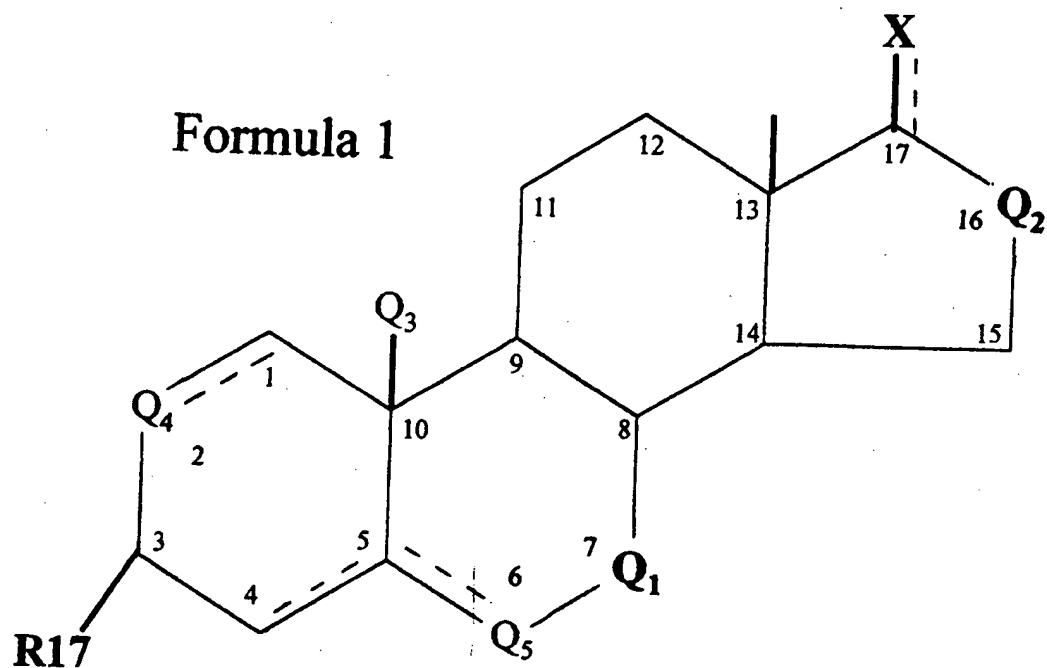
62. A method as recited in claim 61, wherein said viral infection is HIV.

63. A method as recited in any one of claims 57-62, wherein said anti-viral agent comprises at least one protease inhibitor.

64. A method as recited in any one of claims 57-63, wherein said anti-viral agent comprises at least one reverse transcriptase inhibitor.

65. A method as recited in any one of claims 57-64, wherein said anti-viral agent comprises at least one compound selected from the group consisting of:

Formula 1



wherein  $Q_1$  is  $\begin{array}{c} \backslash \\ C \\ / \end{array}$  or  $\begin{array}{c} \backslash \\ C = O \\ / \end{array}$ ,

5 wherein  $Q_2$  is  $\begin{array}{c} \backslash \\ C \\ / \end{array}$ ,  $\begin{array}{c} \backslash \\ C = Y \\ / \end{array}$ , or  $\begin{array}{c} \backslash \\ C \\ | \\ C \\ / \end{array}$

wherein  $Q_3$  is H or  $CH_3$

10 wherein  $Q_4$  is  $\begin{array}{c} / \\ C \\ \backslash \end{array}$ , hydroxyvinylidene, oxy or methyl methylene;

15 wherein  $Q_5$  is  $\begin{array}{c} / \\ C \\ \backslash \end{array}$ , or  $\begin{array}{c} \backslash / \\ C \\ || \\ O \end{array}$

wherein no hydrogen atoms, some hydrogen atoms or all hydrogen atoms are independently replaced by halogen (such as Br, Cl, F or I), hydroxy,  $C_1 - C_6$  alkoxy,  $C_1 - C_6$  alkyl or -S-CN,

20 wherein the broken lines between the 1- and 2-positions, the 4- and 5-positions and the 5- and 6- positions, as well as the broken line adjacent the 17 position and the broken line in the definition of  $Q_2$ , each independently represents a single bond or a double bond,

25 or a metabolite, analog, or precursor of any such compound, or a salt of any such compound, metabolite, analog or precursor.

66. A method as recited in any one of claims 57-65, wherein said at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine comprises IL-4 receptor.

67. A method as recited in any one of claims 57-65, wherein said at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine comprises at least one agonist  
5 or antagonist to a Th<sub>2</sub> cytokine selected from the group consisting of IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13 and GM-CSF.

68. Use of (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine in the manufacture of a medicament for enhancing immune response in a patient in need of such enhancement.

69. Use of (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine in the manufacture of a medicament for treating viral infection, bacterial infection, fungal infection, parasitic infection and/or infectious protein units in a patient in need of such treatment, or for minimizing the likelihood of such infection and/or reducing the potential future adversity of such infection in a patient.

70. Use of (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine in the manufacture of a medicament for providing immunosuppression or immunoregulatory effect in patient in need such effect.

71. A use as recited in any one of claims 68-70, wherein said patient is a mammal.

72. A use as recited in any one of claims 68-71, wherein said viral infection is a retroviral infection.

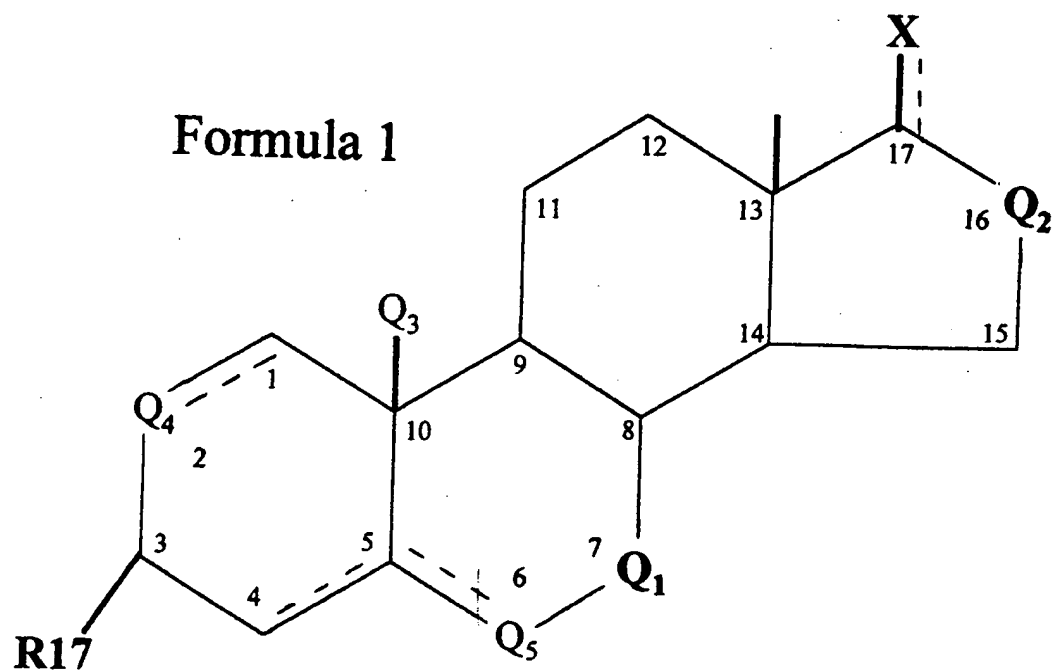
73. A use as recited in claim 72, wherein said viral infection is HIV.

74. A use as recited in any one of claims 68-73, wherein said anti-viral agent comprises at least one protease inhibitor.

75. A use as recited in any one of claims 68-74, wherein said anti-viral agent comprises at least one reverse transcriptase inhibitor.

76. A use as recited in any one of claims 68-75, wherein said anti-viral agent comprises at least one compound selected from the group consisting of:

Formula 1





wherein Q<sub>1</sub> is  $\begin{array}{c} \backslash \\ \text{C} \\ / \end{array}$  or  $\begin{array}{c} \backslash \\ \text{C} = \text{O} \\ / \end{array}$ ,

wherein Q<sub>2</sub> is  $\begin{array}{c} \backslash \\ \text{C} \\ / \end{array}$ ,  $\begin{array}{c} \backslash \\ \text{C} = \text{Y} \\ / \end{array}$ , or  $\begin{array}{c} \backslash \\ \text{C} \\ | \\ \text{C} \\ / \end{array}$

wherein Q<sub>3</sub> is H or CH<sub>3</sub>

wherein Q<sub>4</sub> is  $\begin{array}{c} / \\ \text{C} \\ \backslash \end{array}$ , hydroxyvinylidene, oxy or methyl methylene;

wherein Q<sub>5</sub> is  $\begin{array}{c} / \\ \text{C} \\ \backslash \end{array}$ , or  $\begin{array}{c} \backslash / \\ \text{C} \\ || \\ \text{O} \end{array}$

wherein no hydrogen atoms, some hydrogen atoms or all hydrogen atoms are independently replaced by halogen (such as Br, Cl, F or I), hydroxy, C<sub>1</sub> - C<sub>6</sub> alkoxy, C<sub>1</sub> - C<sub>6</sub> alkyl or -S-CN,

wherein the broken lines between the 1- and 2-positions, the 4- and 5-positions and the 5- and 6-positions, as well as the broken line adjacent the 17 position and the broken line in the definition of Q<sub>2</sub>, each independently represents a single bond or a double bond,

or a metabolite, analog, or precursor of any such compound, or a salt of any such compound, metabolite, analog or precursor.

77. A use as recited in any one of claims 68-76, wherein said at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine comprises IL-4 receptor.

78. A use as recited in any one of claims 68-76, wherein said at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine comprises at least one agonist or antagonist to a Th<sub>2</sub> cytokine selected from the group consisting of IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13 and GM-CSF.

79. A method of reducing proviral DNA in a patient in need of such reduction, comprising administering to said patient (1) at least one anti-viral agent, and (2) at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine.

5 80. A method as recited in claim 79, further comprising administering to said patient at least one Th<sub>2</sub> cytokine.

81. A method as recited in claim 79, further comprising administering to said patient said Th<sub>2</sub> cytokine.

82. A method as recited in claim 81, wherein said Th<sub>2</sub> cytokine is IL-4.

10 83. A method of enhancing immune response in a patient in need of such enhancement, comprising administering to said patient (1) at least one Th<sub>2</sub> cytokine and (2) at least one agonist and/or at least one antagonist to said Th<sub>2</sub> cytokine.

15 84. A method of treating viral infection, bacterial infection, fungal infection, parasitic infection and/or infectious protein units in a patient in need of such treatment, or minimizing the likelihood of such infection and/or reducing the potential future adversity of such infection in a patient, comprising administering to said patient (1) at least one Th<sub>2</sub> cytokine and (2) at least one agonist and/or at least one antagonist to said Th<sub>2</sub> cytokine.

20 85. A method of providing immunosuppression or immunoregulatory effect in patient in need such effect, comprising administering to said patient (1) at least one Th<sub>2</sub> cytokine and (2) at least one agonist and/or at least one antagonist to said Th<sub>2</sub> cytokine.

86. A method as recited in any one of claims 83-85, wherein said Th<sub>2</sub> cytokine is IL-4.

87. A composition comprising:

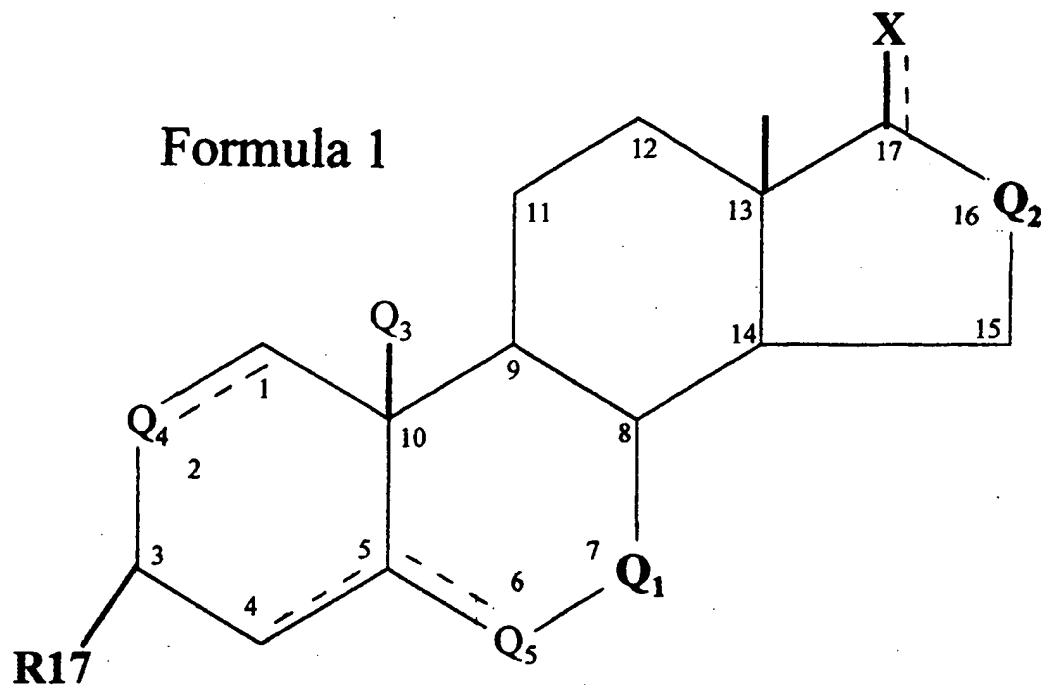
25 (1) at least one anti-viral agent, and  
(2) at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine.

88. A composition as recited in claim 87, wherein said anti-viral agent comprises at least one protease inhibitor.

89. A composition as recited in claim or claim 88, wherein said anti-viral agent comprises at least one reverse transcriptase inhibitor.

30 90. A composition as recited in any one of claims 87-89, wherein said anti-viral agent comprises at least one compound selected from the group consisting of

Formula 1

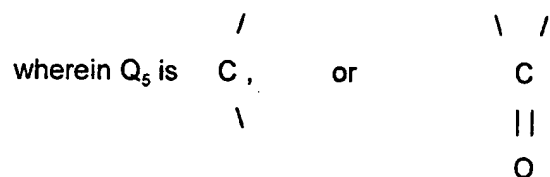


wherein  $Q_1$  is  $\begin{array}{c} \backslash \\ C \\ / \end{array}$  or  $\begin{array}{c} \backslash \\ C=O \\ / \end{array}$ ,

wherein  $Q_2$  is  $\begin{array}{c} \backslash \\ C \\ / \end{array}$ ,  $\begin{array}{c} \backslash \\ C=Y \\ / \end{array}$ , or  $\begin{array}{c} \backslash \\ C \\ | \\ C \\ / \end{array}$

wherein  $Q_3$  is H or  $CH_3$

wherein  $Q_4$  is  $\begin{array}{c} / \\ C \\ \backslash \end{array}$ , hydroxyvinylidene, oxy or methyl m thylene;



wherein no hydrogen atoms, some hydrogen atoms or all hydrogen atoms are independently replaced by halogen (such as Br, Cl, F or I), hydroxy, C<sub>1</sub> - C<sub>6</sub> alkoxy, C<sub>1</sub> - C<sub>6</sub> alkyl or -S-CN,

wherein the broken lines between the 1- and 2-positions, the 4- and 5-positions and the 5- and 6-positions, as well as the broken line adjacent the 17 position and the broken line in the definition of Q<sub>2</sub>, each independently represents a single bond or a double bond,

or a metabolite, analog, or precursor of any such compound, or a salt of any such compound, metabolite, analog or precursor.

91. A composition as recited in any one of claims 87-90, wherein said at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine comprises IL-4 receptor.

5 92. A composition as recited in any one of claims 87-90, wherein said at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine comprises at least one agonist or antagonist to a Th<sub>2</sub> cytokine selected from the group consisting of IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13 and GM-CSF.

93. A kit comprising:

- 10 (1) unit dosages of at least one anti-viral agent, and  
(2) unit dosages of at least one agonist and/or at least one antagonist to a Th<sub>2</sub> cytokine.

FIGURE 1A

ATG GGG CGG CTT TGC ACC AAG TTC CTG ACC TCT GTG GGC TGT CTG -31  
 Met Gly Arg Leu Cys Thr Lys Phe Leu Thr Ser Val Gly Cys Leu -11  
  
 ATT TTG CTG TTG GTG ACT GGA TCT GGG AGC ATC AAG GTC CTG GGT 15  
 Ile Leu Leu Leu Val Thr Gly Ser Gly Ser Ile Lys Val Leu Gly 5  
  
 GAG CCC ACC TGC TTC TCT GAC TAC ATC CGC ACT TCC ACG TGT GAG 60  
 Glu Pro Thr Cys Phe Ser Asp Tyr Ile Arg Thr Ser Thr Cys Glu 20  
  
 TGG TTC CTG GAT AGC GCT GTG GAC TGC AGT TCT CAG CTC TGC CTA 105  
 Trp Phe Leu Asp Ser Ala Val Asp Cys Ser Ser Gln Leu Cys Leu 35  
  
 CAC TAC AGG CTG ATG TTC TTC GAG TTC TCT GAA AAC CTC ACA TGC 150  
 His Tyr Arg Leu Met Phe Phe Glu Phe Ser Glu Asn Leu Thr Cys 50  
  
 ATC CCG AGG AAC AGT GCC AGC ACT GTG TGT GTG TGC CAC ATG GAA 195  
 Ile Pro Arg Asn Ser Ala Ser Thr Val Cys Val Cys His Met Glu 65  
  
 ATG AAT AGG CCG GTC CAA TCA GAC AGA TAC CAG ATG GAA CTG TGG 240  
 Met Asn Arg Pro Val Gln Ser Asp Arg Tyr Gln Met Glu Leu Trp 80  
  
 GCT GAG CAC AGA CAG CTG TGG CAG GGC TCC TTC AGC CCC AGT GGT 285  
 Ala Glu His Arg Gln Leu Trp Gln Gly Ser Phe Ser Pro Ser Gly 95  
  
 AAT GTG AAG CCC CTA GCT CCA GAC AAC CTC ACA CTC CAC ACC AAT 330  
 Asn Val Lys Pro Leu Ala Pro Asp Asn Leu Thr Leu His Thr Asn 110  
  
 GTG TCC GAC GAA TGG CTG CTG ACC TGG AAT AAC CTG TAC CCA TCG 375  
 Val Ser Asp Glu Trp Leu Leu Thr Trp Asn Asn Leu Tyr Pro Ser 125  
  
 AAC AAC TTA CTG TAC AAA GAC CTC ATC TCC ATG GTC AAC ATC TCC 420  
 Asn Asn Leu Leu Tyr Lys Asp Leu Ile Ser Met Val Asn Ile Ser 140  
  
 AGA GAG GAC AAC CCT GCA GAA TTC ATA GTC TAT AAT GTG ACC TAC 465  
 Arg Glu Asp Asn Pro Ala Glu Phe Ile Val Tyr Asn Val Thr Tyr 155  
  
 AAG GAA CCC AGG CTG AGC TTC CCG ATC AAC ATC CTG ATG TCA GGG 510  
 Lys Glu Pro Arg Leu Ser Phe Pro Ile Asn Ile Leu Met Ser Gly 170  
  
 GTC TAC TAT ACG GCG CGT GTG AGG GTC AGA TCC CAG ATA CTC ACT 555  
 Val Tyr Tyr Thr Ala Arg Val Arg Val Arg Ser Gln Ile Leu Thr 185  
  
 GGC ACC TGG AGT GAG TGG AGT CCT AGC ATC ACG TGG TAC AAC CAC 600  
 Gly Thr Trp Ser Glu Trp Ser Pro Ser Ile Thr Trp Tyr Asn His 200  
  
 TTC CAG CTG CCC CTG ATA CAG CGC CTT CCA CTG GGG GTC ACC ATC 645  
 Phe Gln Leu Pro Leu Ile Gln Arg Leu Pro Leu Gly Val Thr Ile 215  
  
 TCC TGC CTC TGC ATC CCG TTG TTT TGC CTG TTC TGT TAC TTC AGC 690  
 Ser Cys Leu Cys Ile Pro Leu Phe Cys Leu Phe Cys Tyr Phe Ser 230  
  
 ATT ACC AAG ATT AAG AAG ATA TGG TGG GAC CAG ATT CCC ACC CCA 735  
 Ile Thr Lys Ile Lys Lys Ile Trp Trp Asp Gln Ile Pro Thr Pro 245

FIGURE 1B

GCA CGC AGT CCC TTG GTG GCC ATC ATC ATT CAG GAT GCA CAG GTG 780  
 Ala Arg Ser Pro Leu Val Ala Ile Ile Ile Gln Asp Ala Gln Val 260  
  
 CCC CTC TGG GAT AAG CAG ACC CGA AGC CAG GAG TCA ACC AAG TAC 825  
 Pro Leu Trp Asp Lys Gln Thr Arg Ser Gln Glu Ser Thr Lys Tyr 275  
  
 CCG CAC TGG AAA ACT TGT CTA GAC AAG CTG CTG CCT TGC TTG CTG 870  
 Pro His Trp Lys Thr Cys Leu Asp Lys Leu Leu Pro Cys Leu Leu 290  
  
 AAG CAC AGA GTA AAG AAG AAG ACA GAC TTC CCG AAG GCT GCC CCA 915  
 Lys His Arg Val Lys Lys Lys Thr Asp Phe Pro Lys Ala Ala Pro 305  
  
 ACC AAG TCT CTC CAG AGT CCT GGA AAG GCA GGC TGG TGT CCC ATG 960  
 Thr Lys Ser Leu Gln Ser Pro Gly Lys Ala Gly Trp Cys Pro Met 320  
  
 GAG GTC AGC AGG ACC GTC CTC TGG CCA GAG AAT GTT AGT GTC AGT 1005  
 Glu Val Ser Arg Thr Val Leu Trp Pro Glu Asn Val Ser Val Ser 335  
  
 GTG GTG CGC TGT ATG GAG CTG TTT GAG GCC CCA GTA CAG AAT GTG 350  
 Val Val Arg Cys Met Glu Leu Phe Glu Ala Pro Val Gln Asn Val 350  
  
 GAG GAG GAA GAA GAT GAG ATA GTC AAA GAG GAC CTG AGC ATG TCA 1095  
 Glu Glu Glu Glu Asp Glu Ile Val Lys Glu Asp Leu Ser Met Ser 365  
  
 CCT GAG AAC AGC GGA GGC TGC GGC TTC CAG GAG AGC CAG GCA GAC 1140  
 Pro Glu Asn Ser Gly Gly Cys Gly Phe Gln Glu Ser Gln Ala Asp 380  
  
 ATC ATG GCT CGG CTC ACT GAG AAC CTG TTT TCC GAC TTG TTG GAG 1185  
 Ile Met Ala Arg Leu Thr Glu Asn Leu Phe Ser Asp Leu Leu Glu 395  
  
 GCT GAG AAT GGG GGC CTT GGC CAG TCA GCC TTG GCA GAG TCA TGC 1230  
 Ala Glu Asn Gly Gly Leu Gly Gln Ser Ala Leu Ala Glu Ser Cys 410  
  
 TCC CCT CTG CCT TCA GGA AGT GGG CAG GCT TCT GTA TCC TGG GCC 1275  
 Ser Pro Leu Pro Ser Gly Ser Gly Gln Ala Ser Val Ser Trp Ala 425  
  
 TGC CTC CCC ATG GGG CCC AGT GAG GAG GCC ACA TGC CAG GTC ACA 1320  
 Cys Leu Pro Met Gly Pro Ser Glu Glu Ala Thr Cys Gln Val Thr 440  
  
 GAG CAG CCT TCA CAC CCA GGC CCT CTT TCA GGC AGC CCA GCC CAG 1365  
 Glu Gln Pro Ser His Pro Gly Pro Leu Ser Gly Ser Pro Ala Gln 455  
  
 AGT GCA CCT ACT CTG GCT TGC ACG CAG GTC CCA CTT GTC CTT GCA 1410  
 Ser Ala Pro Thr Leu Ala Cys Thr Gln Val Pro Leu Val Leu Ala 470  
  
 GAC AAT CCT GCC TAC CGG AGT TTT AGT GAC TGC TGT AGC CCG GCC 1455  
 Asp Asn Pro Ala Tyr Arg Ser Phe Ser Asp Cys Cys Ser Pro Ala 485  
  
 CCA AAT CCT GGA GAG CTG GCT CCA GAG CAG CAG CAG GCT GAT CAT 1500  
 Pro Asn Pro Gly Glu Leu Ala Pro Glu Gln Gln Gln Ala Asp His 500  
  
 CTG GAA GAA GAG GAG CCT CCA AGC CCG GCT GAC CCC CAT TCT TCA 1545  
 Leu Glu Glu Glu Glu Pro Pro Ser Pro Ala Asp Pro His Ser Ser 515



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## FIGURE 1C

GGG CCA CCA ATG CAG CCA GTG GAG AGC TGG GAG CAG ATC CTT CAC 1590  
 Gly Pro Pro Met Gln Pro Val Glu Ser Trp Glu Gln Ile Leu His 530

ATG AGT GTC CTG CAG CAT GGG GCA GCT GCT GGC TCC ACC CCA GCC 1635  
 Met Ser Val Leu Gln His Gly Ala Ala Ala Gly Ser Thr Pro Ala 545

CCT GCC GGT GGC TAC CAG GAG TTT GTG CAG GCA GTG AAG CAG GGT 1680  
 Pro Ala Gly Gly Tyr Gln Glu Phe Val Gln Ala Val Lys Gln Gly 560

GCC GCC CAG GAT CCT GGG GTG CCT GGT GTC AGG CCT TCT GGA GAC 1725  
 Ala Ala Gln Asp Pro Gly Val Pro Gly Val Arg Pro Ser Gly Asp 575

CCC GGT TAC AAG GCC TTC TCG AGC CTG CTC AGC AGC AAT GGC ATC 1770  
 Pro Gly Tyr Lys Ala Phe Ser Ser Leu Leu Ser Ser Asn Gly Ile 590

CGC GGG GAC ACA GCA GCA GCG GGG ACT GAC GAT GGG CAT GGA GGC 1815  
 Arg Gly Asp Thr Ala Ala Ala Gly Thr Asp Asp Gly His Gly Gly 605

TAC AAG CCC TTC CAG AAT CCT GTT CCT AAC CAG TCC CCT AGC TCC 1862  
 Tyr Lys Pro Phe Gln Asn Pro Val Pro Asn Gln Ser Pro Ser Ser 620

GTG CCC TTA TTT ACT TTC GGA CTA GAC ACG GAG CTG TCA CCC AGT 1905  
 Val Pro Leu Phe Thr Phe Gly Leu Asp Thr Glu Leu Ser Pro Ser 635

CCT CTG AAC TCA GAC CCA CCC AAA AGC CCC CCA GAA TGC CTT GGT 1950  
 Pro Leu Asn Ser Asp Pro Pro Lys Ser Pro Pro Glu Cys Leu Gly 650

CTG GAG CTG GGG CTC AAA GGA GGT GAC TGG GTG AAG GCC CCT CCT 1995  
 Leu Glu Leu Gly Leu Lys Gly Gly Asp Trp Val Lys Ala Pro Pro 665

CCT GCA GAT GAG GTG CCC AAG CCC TTT GGG GAT GAC CTG GGC TTT 2040  
 Pro Ala Asp Glu Val Pro Lys Pro Phe Gly Asp Asp Leu Gly Phe 680

GGT ATT GTG TAC TCG TCC CTC ACT TGC CAC TTG TGT GGC CAC CTG 2085  
 Gly Ile Val Tyr Ser Ser Leu Thr Cys His Leu Cys Gly His Leu 695

AAG CAA CAC CAC AGC CAG GAG GAA GGT GGC CAG AGC CCC ATC GTT 2130  
 Lys Gln His His Ser Gln Glu Glu Gly Gly Gln Ser Pro Ile Val 710

GCT AGC CCT GGC TGT GGC TGC TGC TAC GAT GAC AGA TCA CCA TCC 2175  
 Ala Ser Pro Gly Cys Gly Cys Cys Tyr Asp Asp Arg Ser Pro Ser 725

CTG GGG AGC CTC TCG GGG GCC TTG GAA AGC TGT CCT GAG GGA ATA 2220  
 Leu Gly Ser Leu Ser Gly Ala Leu Glu Ser Cys Pro Glu Gly Ile 740

CCA CCA GAA GCC AAC CTC ATG TCA GCA CCC AAG ACA CCC TCA AAC 2265  
 Pro Pro Glu Ala Asn Leu Met Ser Ala Pro Lys Thr Pro Ser Asn 755

TTG TCA GGG GAG GGC AAG GGC CCT GGT CAC TCT CCT GTT CCC AGC 2310  
 Leu Ser Gly Glu Gly Lys Gly Pro Gly His Ser Pro Val Pro Ser 770

CAG ACG ACC GAG GTG CCT GTG GGC GCC CTG GGC ATT GCT GTT TCT 2355  
 Gln Thr Thr Glu Val Pro Val Gly Ala Leu Gly Ile Ala Val Ser 785

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FIGURE 2A

ATG GGG TGG CTT TGC TCT GGG CTC CTG TTC CCT GTG AGC TGC CTG -31  
 Met Gly Trp Leu Cys Ser Gly Leu Leu Phe Pro Val Ser Cys Leu -11

GTC CTG CTG CAG GTG GCA AGC TCT GGG AAC ATG AAG GTC TTG CAG 15  
 Val Leu Leu Gln Val Ala Ser Ser Gly Asn Met Lys Val Leu Gln 5

GAG CCC ACC TGC GTC TCC GAC TAC ATG AGC ATC TCT ACT TGC GAG 60  
 Glu Pro Thr Cys Val Ser Asp Tyr Met Ser Ile Ser Thr Cys Glu 20

TGG AAG ATG AAT GGT CCC ACC AAT TGC AGC ACC GAG CTC CGC CTG 105  
 Trp Lys Met Asn Gly Pro Thr Asn Cys Ser Thr Glu Leu Arg Leu 50

TTG TAC CAG CTG GTT TTT CTG CTC TCC GAA GCC CAC ACG TGT ATC 150  
 Leu Tyr Gln Leu Val Phe Leu Leu Ser Glu Ala His Thr Cys Ile 50

CCT GAG AAC AAC GGA GGC GCG GGG TGC GTG TGC CAC CTG CTC ATG 195  
 Pro Glu Asn Asn Gly Gly Ala Gly Cys Val Cys His Leu Leu Met 65

GAT GAC GTG GTC AGT GCG GAT AAC TAT ACA CTG GAC CTG TGG GCT 240  
 Asp Asp Val Val Ser Ala Asp Asn Tyr Thr Leu Asp Leu Trp Ala 80

GGG CAG CAG CTG CTG TGG AAG GGC TCC TTC AAG CCC AGC GAG CAT 285  
 Gly Gln Gln Leu Leu Trp Lys Gly Ser Phe Lys Pro Ser Glu His 95

GTG AAA CCC AGG GCC CCA GGA AAC CTG ACA GTT CAC ACC AAT GTC 330  
 Val Lys Pro Arg Ala Pro Gly Asn Leu Thr Val His Thr Asn Val 110

TCC GAC ACT CTG CTG CTG ACC TGG AGC AAC CCG TAT CCC CCT GAC 375  
 Ser Asp Thr Leu Leu Leu Thr Trp Ser Asn Pro Tyr Pro Pro Asp 125

AAT TAC CTG TAT AAT CAT CTC ACC TAT GCA GTC AAC ATT TGG AGT 420  
 Asn Tyr Leu Tyr Asn His Leu Thr Tyr Ala Val Asn Ile Trp Ser 140

GAA AAC GAC CCG GCA GAT TTC AGA ATC TAT AAC GTG ACC TAC CTA 465  
 Glu Asn Asp Pro Ala Asp Phe Arg Ile Tyr Asn Val Thr Tyr Leu 155

GAA CCC TCC CTC CGC ATC GCA GCC AGC ACC CTG AAG TCT GGG ATT 510  
 Glu Pro Ser Leu Arg Ile Ala Ala Ser Thr Leu Lys Ser Gly Ile 170

TCC TAC AGG GCA CGG GTG AGG GCC TGG GCT CAG TGC TAT AAC ACC 555  
 Ser Tyr Arg Ala Arg Val Arg Ala Trp Ala Gln Cys Tyr Asn Thr 185

ACC TGG AGT GAG TGG AGC CCC AGC ACC AAG TGG CAC AAC TCC TAC 600  
 Thr Trp Ser Glu Trp Ser Pro Ser Thr Lys Trp His Asn Ser Tyr 200

AGG GAG CCC TTC GAG CAG CAC CTC CTG CTG GGC GTC AGC GTT TCC 645  
 Arg Glu Pro Phe Glu Gln His Leu Leu Leu Gly Val Ser Val Ser 215

AGG GAG CCC TTC GAG CAG CAC CTC CTG CTG GGC GTC AGC GTT TCC 645  
 Arg Glu Pro Phe Glu Gln His Leu Leu Leu Gly Val Ser Val Ser 215

TGC ATT GTC ATC CTG GCC GTC TGC CTG TTG TGC TAT GTC AGC ATC 690  
Cys Ile Val Ile Leu Ala Val Cys Leu Leu Cys Tyr Val Ser Ile 230

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FIGURE 2B

ACC AAG ATT AAG AAA GAA TGG TGG GAA CAG ATT CCC AAC CCA GCC 735  
 Thr Lys Ile Lys Lys Glu Trp Trp Asp Gln Ile Pro Asn Pro Ala 245

CGC AGC CGC CTC GTG GCT ATA ATA ATC CAG GAT GCT CAG GGG TCA 780  
 Arg Ser Arg Leu Val Ala Ile Ile Ile Gln Asp Ala Gln Gly Ser 260

CAG TGG GAG AAG CGG TCC CGA GGC CAG GAA CCA GCC AAG TGC CCA 825  
 Gln Trp Glu Lys Arg Ser Arg Gly Gln Glu Pro Ala Lys Cys Pro 275

CAC TGG AAG AAT TGT CTT ACC AAG CTC TTG CCC TGT TTT CTG GAG 870  
 His Trp Lys Asn Cys Leu Thr Lys Leu Leu Pro Cys Phe Leu Glu 290

CAC AAC ATG AAA AGG GAT GAA GAT CCT CAC AAG GCT GCC AAA GAG 915  
 His Asn Met Lys Arg Asp Glu Asp Pro His Lys Ala Ala Lys Glu 305

ATG CCT TTC CAG GGC TCT GGA AAA TCA GCA TGG TGC CCA GTG GAG 960  
 Met Pro Phe Gln Gly Ser Gly Lys Ser Ala Trp Cys Pro Val Glu 320

ATC AGC AAG ACA GTC CTC TGG CCA GAG AGC ATC AGC GTG GTG CGA 1005  
 Ile Ser Lys Thr Val Leu Trp Pro Glu Ser Ile Ser Val Val Arg 335

TGT GTG GAG TTG TTT GAG GCC CCG GTG GAG TGT GAG GAG GAG GAG 1050  
 Cys Val Glu Leu Phe Glu Ala Pro Val Glu Cys Glu Glu Glu Glu 350

GAG GTA GAG GAA GAA AAA GGG AGC TTC TGT GCA TCG CCT GAG AGC 1095  
 Glu Val Glu Glu Glu Lys Gly Ser Phe Cys Ala Ser Pro Glu Ser 365

AGC AGG GAT GAC TTC CAG GAG GGA AGG GAG GGC ATT GTG GCC CGG 1140  
 Ser Arg Asp Asp Phe Gln Glu Gly Arg Glu Gly Ile Val Ala Arg 380

CTA ACA GAG AGC CTG TTC CTG GAC CTG CTC GGA GAG GAG AAT GGG 1185  
 Leu Thr Glu Ser Leu Phe Leu Asp Leu Leu Gly Glu Glu Asn Gly 395

GGC TTT TGC CAG CAG GAC ATG GGG GAG TCA TGC CTT CTT CCA CCT 1230  
 Gly Phe Cys Gln Gln Asp Met Gly Glu Ser Cys Leu Leu Pro Pro 410

TCG GGA AGT ACG AGT GCT CAC ATG CCC TGG GAT GAG TTC CCA AGT 1275  
 Ser Gly Ser Thr Ser Ala His Met Pro Trp Asp Glu Phe Pro Ser 425

GCA GGG CCC AAG GAG GCA CCT CCC TGG GGC AAG GAG CAG CCT CTC 1320  
 Ala Gly Pro Lys Glu Ala Pro Pro Trp Gly Lys Glu Gln Pro Leu 440

CAC CTG GAG CCA AGT CCT CCT GCC AGC CCG ACC CAG AGT CCA CTC 1365  
 His Leu Glu Pro Ser Pro Pro Ala Ser Pro Thr Gln Ser Pro Leu 455

AAC CTG ACT TGC ACA GAG ACG CCC CTC GTC ATC GCA GGC AAC CCT 1410  
 Asn Leu Thr Cys Thr Glu Thr Pro Leu Val Ile Ala Gly Asn Pro 470

GCT TAC CGC AGC TTC AGC AAC TCC CTG AGC CAG TCA CCG TGT CCC 1455  
 Ala Tyr Arg Ser Phe Ser Asn Ser Leu Ser Gln Ser Pro Cys Pro 485

AGA GAG CTG GGT CCA GAC CCA CTG CTG GCC AGA CAC CTG GAG GAA 1500  
 Arg Glu Leu Gly Pro Asp Pro Leu Leu Ala Arg His Leu Glu Glu 500

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FIGURE 2C

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| GTA | GAA | CCC | GAG | ATG | CCC | TGT | GTC | CCC | CAG | CTC | TCT | GAG | CCA | ACC | 1545 |
| Val | Glu | Pro | Glu | Met | Pro | Cys | Val | Pro | Gln | Leu | Ser | Glu | Pro | Thr | 515  |
| ACT | GTG | CCC | CAA | CCT | GAG | CCA | GAA | ACC | TGG | GAG | CAG | ATC | CTC | CGC | 1590 |
| Thr | Val | Pro | Gln | Pro | Glu | Pro | Glu | Thr | Trp | Glu | Gln | Ile | Leu | Arg | 530  |
| CGA | AAT | GTC | CTC | CAG | CAT | GGG | GCA | GCT | GCA | GCC | CCC | GTC | TCG | GCC | 1635 |
| Arg | Asn | Val | Leu | Gln | His | Gly | Ala | Ala | Ala | Ala | Pro | Val | Ser | Ala | 545  |
| CCC | ACC | AGT | GGC | TAT | CAG | GAG | TTT | GTA | CAT | GCG | GTG | GAG | CAG | GGT | 1680 |
| Pro | Thr | Ser | Gly | Tyr | Gln | Glu | Phe | Val | His | Ala | Val | Glu | Gln | Gly | 560  |
| GGC | ACC | CAG | GCC | AGT | GCG | GTG | GTG | GGC | TTG | GGT | CCC | CCA | GGA | GAG | 1725 |
| Gly | Thr | Gln | Ala | Ser | Ala | Val | Val | Gly | Leu | Gly | Pro | Pro | Gly | Glu | 575  |
| GCT | GGT | TAC | AAG | GCC | TTC | TCA | AGC | CTG | CTT | GCC | AGC | AGT | GCT | GTG | 1770 |
| Ala | Gly | Tyr | Lys | Ala | Phe | Ser | Ser | Leu | Leu | Ala | Ser | Ser | Ala | Val | 590  |
| TCC | CCA | GAG | AAA | TGT | GGG | TTT | GGG | GCT | AGC | AGT | GGG | GAA | GAG | GGG | 1815 |
| Ser | Pro | Glu | Lys | Cys | Gly | Phe | Gly | Ala | Ser | Ser | Gly | Glu | Glu | Gly | 605  |
| TAT | AAG | CCT | TTC | CAA | GAC | CTC | ATT | CCT | GGC | TGC | CCT | GGG | GAC | CCT | 1860 |
| Tyr | Lys | Pro | Phe | Gln | Asp | Leu | Ile | Pro | Gly | Cys | Pro | Gly | Asp | Pro | 620  |
| GCC | CCA | GTC | CCT | GTC | CCC | TTG | TTC | ACC | TTT | GGA | CTG | GAC | AGG | GAG | 1905 |
| Ala | Pro | Val | Pro | Val | Pro | Leu | Phe | Thr | Phe | Gly | Leu | Asp | Arg | Glu | 635  |
| CCA | CCT | CGC | AGT | CCG | CAG | AGC | TCA | CAT | CTC | CCA | AGC | AGC | TCC | CCA | 1950 |
| Pro | Pro | Arg | Ser | Pro | Gln | Ser | Ser | His | Leu | Pro | Ser | Ser | Ser | Pro | 650  |
| GAG | CAC | CTG | GGT | CTG | GAG | CCG | GGG | GAA | AAG | GTA | GAG | GAC | ATG | CCA | 1995 |
| Glu | His | Leu | Gly | Leu | Glu | Pro | Gly | Glu | Lys | Val | Glu | Asp | Met | Pro | 665  |
| AAG | CCC | CCA | CTT | CCC | CAG | GAG | CAG | GCC | ACA | GAC | CCC | CTT | GTG | GAC | 2040 |
| Lys | Pro | Pro | Leu | Pro | Gln | Glu | Gln | Ala | Thr | Asp | Pro | Leu | Val | Asp | 680  |
| AGC | CTG | GGC | AGT | GGC | ATT | GTC | TAC | TCA | GCC | CTT | ACC | TGC | CAC | CTG | 2085 |
| Ser | Leu | Gly | Ser | Gly | Ile | Val | Tyr | Ser | Ala | Leu | Thr | Cys | His | Leu | 695  |
| TGC | GGC | CAC | CTG | AAA | CAG | TGT | CAT | GGC | CAG | GAG | GAT | GGT | GGC | CAG | 2130 |
| Cys | Gly | His | Leu | Lys | Gln | Cys | His | Gly | Gln | Glu | Asp | Gly | Gly | Gln | 710  |
| ACC | CCT | GTC | ATG | GCC | AGT | CCT | TGC | TGT | GGC | TGC | TGC | TGT | GGA | GAC | 2175 |
| Thr | Pro | Val | Met | Ala | Ser | Pro | Cys | Cys | Gly | Cys | Cys | Cys | Gly | Asp | 725  |
| AGG | TCC | TCG | CCC | CCT | ACA | ACC | CCC | CTG | AGG | GCC | CCA | GAC | CCC | TCT | 2220 |
| Arg | Ser | Ser | Pro | Pro | Thr | Thr | Pro | Leu | Arg | Ala | Pro | Asp | Pro | Ser | 740  |
| CCA | GGT | GGG | GTT | CCA | CTG | GAG | GCC | AGT | CTG | TGT | CCG | GCC | TCC | CTG | 2265 |
| Pro | Gly | Gly | Val | Pro | Leu | Glu | Ala | Ser | Leu | Cys | Pro | Ala | Ser | Leu | 755  |
| GCA | CCC | TCG | GGC | ATC | TCA | GAG | AAG | AGT | AAA | TCC | TCA | TCA | TCC | TTC | 2355 |
| Ala | Pro | Ser | Gly | Ile | Ser | Glu | Lys | Ser | Lys | Ser | Ser | Ser | Ser | Phe | 770  |

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## FIGURE 2D

CAT CCT GCC CCT GGC AAT GCT CAG AGC TCA AGC CAG ACC CCC AAA 2310  
His Pro Ala Pro Gly Asn Ala Gln Ser Ser Ser Gln Thr Pro Lys 785

ATC GTG AAC TTT GTC TCC GTG GGA CCC ACA TAC ATG AGG GTC TCT 2400  
Ile Val Asn Phe Val Ser Val Gly Pro Thr Tyr Met Arg Val Ser 800

Figure 3 (A)

| Patient PO52R<br>No. of Days | Ref. Ranges                      | Treatment A |      |      |      |      |      |      |  |  |  |
|------------------------------|----------------------------------|-------------|------|------|------|------|------|------|--|--|--|
|                              |                                  | 0           | 4    | 14   | 21   | 28   | 35   | 42   |  |  |  |
| Glucose                      | 85-110 mg/dl                     | 49          | 55   |      |      |      |      |      |  |  |  |
| Protein Bound Glucose        | < 1.20 mg/gm                     | 0.81        | 0.7  |      |      |      |      |      |  |  |  |
| Bun                          | 6-25 mg/dl                       | 27          | 19   |      |      |      |      |      |  |  |  |
| Creatinine                   | 0.5-1.2 mg/dl                    | 0.9         | 1    |      |      |      |      |      |  |  |  |
| Bun/Creatinine Ratio         | 10-28 Ratio                      | 30          | 19   |      |      |      |      |      |  |  |  |
| SGOT                         | 1-45 u/l                         | 23          | 22   |      |      |      |      |      |  |  |  |
| SGPT                         | 1-45 u/l                         | 26          | 25   |      |      |      |      |      |  |  |  |
| LDH                          | 100-225 u/l                      | 159         | 177  |      |      |      |      |      |  |  |  |
| GGTP                         | 5-52 u/l                         | 17          | 21   |      |      |      |      |      |  |  |  |
| Bilirubin, Total             | 0.1-1.5 mg/dl                    | 0.6         | 0.5  |      |      |      |      |      |  |  |  |
| Alkaline Phos. Total         | 30-125 u/l                       | 56          | 61   |      |      |      |      |      |  |  |  |
| Calcium                      | 8.7-10.5 mg/dl                   | 9.6         | 10.3 |      |      |      |      |      |  |  |  |
| Phosphorus                   | 2.5-4.5 mg/dl                    | 3.6         | 4.1  |      |      |      |      |      |  |  |  |
| Magnesium, Serum             | 1.3-2.3 mg/dl                    | 2.2         | 1.9  |      |      |      |      |      |  |  |  |
| Sodium                       | 135-148 Meg/l                    | 142         | 140  |      |      |      |      |      |  |  |  |
| Potassium                    | 3.5-5.5 Meg/l                    | 4.2         | 4.4  |      |      |      |      |      |  |  |  |
| Chloride                     | 95-107 Meg/l                     | 108         | 100  |      |      |      |      |      |  |  |  |
| Uric Acid                    | 2.5-6.0 mg/dl                    | 6.1         | 4.7  |      |      |      |      |      |  |  |  |
| Triglycerides                | 35-160 mg/dl                     | 112         | 198  |      |      |      |      |      |  |  |  |
| Cholesterol                  | 135-199 mg/dl                    | 155         | 195  |      |      |      |      |      |  |  |  |
| HDL Cholesterol              | 30-85 mg/dl                      | 34          | 33   |      |      |      |      |      |  |  |  |
| LDL Cholesterol              | <130 mg/dl                       | 103         | 130  |      |      |      |      |      |  |  |  |
| Total Protein                | 6.2-8.0 g/dl                     | 8           | 9.1  |      |      |      |      |      |  |  |  |
| Albumin                      | 4.1-5.4 g/dl                     | 4.3         | 4.8  |      |      |      |      |      |  |  |  |
| Globulin                     | 1.6-3.3 gm/dl                    | 4.7         | 4.3  |      |      |      |      |      |  |  |  |
| A/G Ratio                    | 1.4-3.1 Ratio                    | 1.2         | 1.1  |      |      |      |      |      |  |  |  |
| Iron, Total Serum            | 40-180 mcg/dl                    | 80          | 83   |      |      |      |      |      |  |  |  |
| TIBC                         | 250-390 mcg/dl                   | 299         | 331  |      |      |      |      |      |  |  |  |
| Saturation                   | 15-50 Percent                    | 27          | 25   |      |      |      |      |      |  |  |  |
| WBC                          | 4.0-11.0 X 10 <sup>3</sup> /Cumm | 5.7         | 5.5  | 5.9  | 4.7  | 4.5  | 4.5  | 4.3  |  |  |  |
| RBC                          | 3.9-5.1 X 10 <sup>6</sup> /Cumm  | 5.1         | 5.21 | 5.25 | 4.94 | 4.75 | 4.74 | 4.86 |  |  |  |
| Hemoglobin                   | 12.0-18.0 Grams/dl               | 15.7        | 16.3 | 16.1 | 15.7 | 14.7 | 14.6 | 15   |  |  |  |
| Hematocrit                   | 38-46%                           | 46.7        | 46.9 | 47.7 | 44.6 | 42.1 | 42.9 | 42.9 |  |  |  |
| MCV                          | 82-97 Cubic Mic.                 | 92          | 90   | 91   | 90   | 89   | 90   | 88   |  |  |  |
| MCH                          | 27-34 Picograms                  | 30.9        | 31.3 | 30.6 | 31.8 | 31   | 30.8 | 30.8 |  |  |  |
| MCHC                         | 32-36%                           | 33.7        | 34.8 | 33.7 | 35.2 | 34.9 | 34   | 34.9 |  |  |  |
| RDW                          | 11.8-15.2%                       | 7.5         | 16.5 | 15.9 | 16   | 15.1 | 14.7 | 14   |  |  |  |
| MPV                          | 5.2-11.1 FL                      | 8.5         | 8.7  | 8.5  | 8.7  | 8.5  | 8.9  | 8.7  |  |  |  |
| Platelet Count               | 150-400 X 10 <sup>3</sup> /Cumm  | 89          | 85   | 109  | 83   | 90   | 85   | 83   |  |  |  |
| Polys                        | 50-70%                           | 39          | 42   | 57   | 54   | 43   | 51   | 43   |  |  |  |
| Lymphocytes                  | 15-50%                           | 45          | 44   | 31   | 36   | 40   | 37   | 45   |  |  |  |
| Bands                        | 0-5%                             | 0           | 0    | 0    | 0    | 0    | 0    | 0    |  |  |  |
| Monocytes                    | 0-10%                            | 15          | 14   | 10   | 8    | 14   | 11   | 11   |  |  |  |
| Eosinophils                  | 0-5%                             | 1           | 1    | 1    | 1    | 1    | 1    | 1    |  |  |  |
| Basophils                    | 0-5%                             | 0           | 0    | 1    | 1    | 2    | 0    | 0    |  |  |  |
| Specific Gravity             | 1.005-1.035                      | 1.025       | 1.02 |      |      |      |      |      |  |  |  |

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Figure 3 (B)

| Patient P052R                   |  | Ref. Ranges          |  | Treatment A |       |        |        |          |        |        |  |
|---------------------------------|--|----------------------|--|-------------|-------|--------|--------|----------|--------|--------|--|
| No. of Days                     |  |                      |  | 0           | 4     | 14     | 21     | 28       | 35     | 42     |  |
| Color                           |  |                      |  | Yellow      | Straw |        |        |          |        |        |  |
| Appearance                      |  |                      |  | Clear       | Clear |        |        |          |        |        |  |
| PH                              |  | 4.5-7.5              |  |             | 5     |        |        |          |        |        |  |
| Glucose, Urine                  |  | Negative             |  | Neg         | Neg   |        |        |          |        |        |  |
| Protein, Urine                  |  | Negative             |  | Neg         | Neg   |        |        |          |        |        |  |
| Acetone, Urine                  |  | Negative             |  | Neg         | Neg   |        |        |          |        |        |  |
| Occult Blood                    |  | Negative             |  | Neg         | Neg   |        |        |          |        |        |  |
| Bilirubin                       |  | Negative             |  | Neg         | Neg   |        |        |          |        |        |  |
| Urobilinogen                    |  | 0.2-1.0 mg/dl        |  | 0.2         | 0.2   |        |        |          |        |        |  |
| Leukocyte Esterase              |  | Negative             |  | Neg         | Neg   |        |        |          |        |        |  |
| Nitrite                         |  | Negative             |  | Neg         | Neg   |        |        |          |        |        |  |
| WBC Urine                       |  | 0-5/HPF              |  | 0           | 0     |        |        |          |        |        |  |
| RBC, Urine                      |  | 0-3/HPF              |  | 0           | 0     |        |        |          |        |        |  |
| Epithelial                      |  | /HPF                 |  | 0           | 0     |        |        |          |        |        |  |
| Bacteria                        |  | 0/HPF                |  | 0           | 0     |        |        |          |        |        |  |
| Casts                           |  | None/LPF             |  | None        | None  |        |        |          |        |        |  |
| Urine, Microscopic              |  |                      |  |             |       |        |        |          |        |        |  |
| Direct Lymphocyte Count         |  | 1100-3000 Cells/Cumm |  | 2007        | 2175  | 1814   | 1460   | 1577     | 1700   | 1504   |  |
| Total T (CD3)                   |  | 51-87 Percent        |  | 86          | 91    | 93     | 87     | 88       | 84     | 89     |  |
| Total T (Absolute #)            |  | 510-3240 #/ul        |  | 1716        | 1983  | 1681   | 1266   | 1392     | 1428   | 1334   |  |
| Helper T (CD4)                  |  | 31-59 Percent        |  | 10          | 11    | 12     | 11     | 11       | 9      | 10     |  |
| Helper T (Absolute #)           |  | 537-1571 #/ul        |  | 202         | 237   | 212    | 165    | 172      | 156    | 142    |  |
| Suppressor T (CD8)              |  | 13-33 Percent        |  | 69          | 79    | 82     | 73     | 76       | 67     | 74     |  |
| Suppressor T (Abs #)            |  | 235-753 #/ul         |  | 1387        | 1713  | 1485   | 1064   | 1197     | 1138   | 1113   |  |
| Helper/Suppressor               |  | 1.2-3.8              |  | 0.1         | 0.1   | 0.1    | 0.2    | 0.1      | 0.1    | 0.1    |  |
| Chol/HDL Risk Ratio             |  | Ratio                |  | 4.5         | 5.9   |        |        |          |        |        |  |
| HIV-1 RNA by PCR Q <sub>t</sub> |  | <400 Copies/ml       |  | 15384       | 52972 | 157812 | 122532 | 159402   | 121591 | 573538 |  |
| HIV RNA by PCR Log 10           |  | <2.6 Copies/ml       |  | 4.2         | 4.7   | 5.2    | 5.1    | 5.2      | 5.1    | 5.8    |  |
| IgG Serum                       |  | 800-1800 mg/dl       |  | 2550        | 2230  |        |        |          |        |        |  |
| IgA Serum                       |  | 90-450 mg/dl         |  | 362         | 333   |        |        |          |        |        |  |
| IgM Serum                       |  | 60-280 mg/dl         |  | 528         | 458   |        |        |          |        |        |  |
| Interferon Gamma                |  |                      |  | 0.1         | 0     |        |        |          |        |        |  |
| Interleukin-2                   |  | <30 pg/ml            |  | <30         | <30   |        |        |          |        |        |  |
| Interleukin-12                  |  | <10                  |  | <10         | <10   |        |        |          |        |        |  |
| Interleukin-4                   |  |                      |  |             |       |        |        |          |        |        |  |
| IL-10                           |  |                      |  |             |       |        |        |          |        |        |  |
| Toxo IgG Serum                  |  |                      |  | 7.3         | 5.1   |        |        |          |        |        |  |
| Toxo IgM Serum                  |  |                      |  |             |       |        |        | 1        |        |        |  |
| Hep B Surf Antigen              |  |                      |  |             |       |        |        | 0.28     |        |        |  |
| Hep C Antibody                  |  |                      |  |             |       |        |        | Negative |        |        |  |
| Hep B Surf Antibody             |  |                      |  |             |       |        |        | Negative |        |        |  |
| Hep A Total (IGG + IGM)         |  |                      |  |             |       |        |        | Positive |        |        |  |
| Hep B Core AB, Total            |  |                      |  |             |       |        |        | Positive |        |        |  |
| Hepatitis A, IGM                |  |                      |  |             |       |        |        | Negative |        |        |  |
| HBSAB Units, Qual.              |  |                      |  |             |       |        |        | Negative |        |        |  |
| Neutrophils                     |  | 50-70 FL             |  |             |       |        |        | >15      |        |        |  |
| HIV 1 RNA by bDNA-Nichols       |  | <500 Copies/mL       |  |             |       |        |        |          |        |        |  |

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Figure 3(C)

| Patient P052R<br>No. of Days | TREATMENT A |      |      |      | TREATMENT B |      |      | TREATMENT C |      |
|------------------------------|-------------|------|------|------|-------------|------|------|-------------|------|
|                              | 49          | 57   | 92   | 190  | 194         | 202  | 208  | 208         | 208  |
| Glucose                      |             |      |      |      |             |      |      |             |      |
| Protein Bound Glucose        |             |      |      |      |             |      |      |             |      |
| Bun                          |             |      |      |      |             |      |      |             |      |
| Creatinine                   |             |      |      |      |             |      |      |             |      |
| Bun/Creatinine Ratio         |             |      |      |      |             |      |      |             |      |
| SGOT                         |             |      |      |      |             |      |      |             |      |
| SGPT                         |             |      |      |      |             |      |      |             |      |
| LDH                          |             |      |      |      |             |      |      |             |      |
| GGT                          |             |      |      |      |             |      |      |             |      |
| Bilirubin, Total             |             |      |      |      |             |      |      |             |      |
| Alkaline Phos. Total         |             |      |      |      |             |      |      |             |      |
| Calcium                      |             |      |      |      |             |      |      |             |      |
| Phosphorus                   |             |      |      |      |             |      |      |             |      |
| Magnesium, Serum             |             |      |      |      |             |      |      |             |      |
| Sodium                       |             |      |      |      |             |      |      |             |      |
| Potassium                    |             |      |      |      |             |      |      |             |      |
| Chloride                     |             |      |      |      |             |      |      |             |      |
| Uric Acid                    |             |      |      |      |             |      |      |             |      |
| Triglycerides                |             |      |      |      |             |      |      |             |      |
| Cholesterol                  |             |      |      |      |             |      |      |             |      |
| HDL Cholesterol              |             |      |      |      |             |      |      |             |      |
| LDL Cholesterol              |             |      |      |      |             |      |      |             |      |
| Total Protein                |             |      |      |      |             |      |      |             |      |
| Albumin                      |             |      |      |      |             |      |      |             |      |
| Globulin                     |             |      |      |      |             |      |      |             |      |
| A/G Ratio                    |             |      |      |      |             |      |      |             |      |
| Iron, Total Serum            |             |      |      |      |             |      |      |             |      |
| TIBC                         |             |      |      |      |             |      |      |             |      |
| Saturation                   |             |      |      |      |             |      |      |             |      |
| WBC                          | 4.1         | 5.2  | 5.9  | 5.4  | 5.2         | 6.5  | 6.3  | 6.3         | 6.3  |
| RBC                          | 5.01        | 5.27 | 5.07 | 3.75 | 3.95        | 4    | 4.41 | 4.41        | 4.41 |
| Hemoglobin                   | 15.7        | 15.7 | 15.9 | 14.1 | 15.5        | 15.4 | 18.1 | 18.1        | 18.1 |
| Hematocrit                   | 45.4        | 47.2 | 48.9 | 42.9 | 44.2        | 44.9 | 48.8 | 48.8        | 48.8 |
| MCV                          | 90          | 90   | 92   | 114  | 112         | 112  | 111  | 111         | 111  |
| MCH                          | 31.2        | 29.8 | 31.3 | 37.5 | 39.3        | 38.5 | 36.5 | 36.5        | 36.5 |
| MCHC                         | 34.5        | 33.2 | 33.9 | 32.8 | 35.1        | 34.2 | 33   | 33          | 33   |
| RDW                          | 14.8        | 14   | 19   | 13.7 | 13.1        | 12.6 | 13.2 | 13.2        | 13.2 |
| MPV                          | 8.9         | 9.4  | 9.3  | 8.2  | 8.5         | 7.8  | 8.6  | 8.6         | 8.6  |
| Platelet Count               | 81          | 88   | 58   | 179  | 128         | 132  | 139  | 139         | 139  |
| Polys                        | 52          | 56   | 57   |      |             |      |      |             |      |
| Lymphocytes                  | 32          | 32   | 30   | 43   | 31          | 31   | 30   | 30          | 30   |
| Bands                        | 0           | 0    | 0    |      |             |      |      |             |      |
| Monocytes                    | 13          | 9    | 10   | 12   | 13          | 10   | 8    | 8           | 8    |
| Eosinophils                  | 2           | 1    | 2    | 1    | 1           | 1    | 1    | 1           | 1    |
| Basophils                    | 1           | 2    | 1    | 0    | 0           | 1    | 0    | 0           | 0    |
| Specific Gravity             |             |      |      |      |             |      |      |             |      |



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FIGURE 3(D)

| Patient P052R             | 49     | 57    | 92      | 190  | 194   | TREATMENT B | TREATMENT C |
|---------------------------|--------|-------|---------|------|-------|-------------|-------------|
| No. of Days               |        |       |         |      |       | 202         | 208         |
| Color                     |        |       |         |      |       |             |             |
| Appearance                |        |       |         |      |       |             |             |
| PH                        |        |       |         |      |       |             |             |
| Glucose, Urine            |        |       |         |      |       |             |             |
| Protein, Urine            |        |       |         |      |       |             |             |
| Acetone, Urine            |        |       |         |      |       |             |             |
| Occult Blood              |        |       |         |      |       |             |             |
| Bilirubin                 |        |       |         |      |       |             |             |
| Urobilinogen              |        |       |         |      |       |             |             |
| Leukocyte Esterase        |        |       |         |      |       |             |             |
| Nitrite                   |        |       |         |      |       |             |             |
| WBC Urine                 |        |       |         |      |       |             |             |
| RBC, Urine                |        |       |         |      |       |             |             |
| Epithelial                |        |       |         |      |       |             |             |
| Bacteria                  |        |       |         |      |       |             |             |
| Casts                     |        |       |         |      |       |             |             |
| Urine, Microscopic        |        |       |         |      |       |             |             |
| Direct Lymphocyte Count   | 1248   | 1704  | 1732    | 1828 | 1593  | 1888        |             |
| Total T (CD3)             | 94     | 89    | 87      | 86   | 88    | 85          |             |
| Total T (Absolute #)      | 1174   | 1508  | 1504    | 1567 | 1402  | 1609        |             |
| Helper T (CD4)            | 12     | 13    | 12      | 13   | 11    | 15          |             |
| Helper T (Absolute #)     | 152    | 218   | 203     | 245  | 177   | 276         |             |
| Suppressor T (CD8)        | 83     | 70    | 69      | 70   | 73    | 67          |             |
| Suppressor T (Abs #)      | 1035   | 1195  | 1200    | 1276 | 1167  | 1255        |             |
| Helper/Suppressor         | 0.1    | 0.2   | 0.2     | 0.2  | 0.2   | 0.2         |             |
| CholHDL Risk Ratio        |        |       |         |      | 7.8   | 6.1         | 5           |
| HIV-1 RNA by PCR Q1       | 193073 | 10096 | 1481262 | 2960 | 77626 | 7467        | <400        |
| HIV RNA by PCR Log 10     | 5.3    |       | 6.2     | 3.5  | 4.9   | 3.9         | <2.6        |
| IgG Serum                 |        |       |         |      | 1920  | 1650        | 1590        |
| IgA Serum                 |        |       |         |      | 689   | 437         | 408         |
| IgM Serum                 |        |       |         |      | 512   | 357         | 417         |
| Interferon Gamma          |        |       |         |      | 0     |             |             |
| Interleukin-2             |        |       |         |      |       |             |             |
| Interleukin-12            |        |       |         |      |       |             |             |
| Interleukin-4             |        |       |         |      | 0     |             |             |
| IL-10                     |        |       |         |      |       |             |             |
| Toxo IgG Serum            |        |       |         |      |       |             |             |
| Toxo IgM Serum            |        |       |         |      |       |             |             |
| Hep B Surf Antigen        |        |       |         |      |       |             |             |
| Hep C Antibody            |        |       |         |      |       |             |             |
| Hep B Surf Antibody       |        |       |         |      |       |             |             |
| Hep A Total (IGG + IGM)   |        |       |         |      |       |             |             |
| Hep B Core AB, Total      |        |       |         |      |       |             |             |
| Hepatitis A, IGM          |        |       |         |      |       |             |             |
| HBSAB Units, Qual.        |        |       |         |      |       |             |             |
| Neutrophils               |        |       |         | 44   | 55    | 59          | 61          |
| HIV 1 RNA by bDNA-Nichols |        |       |         | 3203 |       |             | 2107        |